Novel Strategies for Secondary Stroke Prevention -

Exploring the Use of Pioglitazone Therapy

Using a Mixed Methods Approach

A thesis by

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Declaration

The thesis work was performed by me for a submission of a PhD degree in the University Division of Cardiovascular and Medical Science at the Queen Elizabeth University Hospital.

In all thesis chapters, the statistical analyses were done entirely by me. In chapters 2 and 3, all statistical analyses and GRADE evidence for meta-analyses were conducted using Review Manger and GRADEPro software by me. The searching of databases for eligible studies in chapter 3 was performed by me with help of a second independent researcher, John McLoughlin.

In chapter 4, the PIOSurvey questions were designed by me with advice from my supervisor and Dr. Terence Quinn and Dr. Satu Baylan. All analysis performed using the BOS software was done by me.

In chapter 5, the audiotaped interviews were transcribed verbatim by Pamela McKenzie. The focus groups interviews were led by Professor Jesse Dawson, Dr. Martin O'Neill, Mr. Alexander Smith and Dr. Jonathan Hewitt. All other data coding to created themes and subthemes for analysis was done by me.

In chapter 6, the thesis vision, novelty and future directions is my own work.

Finally, I declare that except where explicit reference is made to the contribution of others, that this thesis writing is the result of my own work and has not been submitted for any degree at the University of Glasgow or any other organisation.

The thesis works have been presented at international and national meetings including the Scottish Society Physician Inverness (2017), UK Stroke Forum in Liverpool and Telford (2017; 2019), the Association of Physicians of Great Britain and Ireland in Glasgow (2019), the U21 health sciences of International Doctoral student experience and transferability of Doctoral training Forum (2019), the Three Minute Thesis competition at the University of Glasgow (2020) and the European Stroke Organisation Congress in Milan and Vienna (2019; 2020).

HALA FOUAD AZHARI

Table of Contents

Index of Tables

Index of Figures

List of Publications

Chapter 5

1. O'Neill M, Hewitt J, Smith A, Azhari H and Dawson J. Post Stroke Hypertension Management: A Qualitative Study. (AA-19-1028). The Article manuscripts is submitted at Oxford University Press Age and Ageing Journal for publication.

2. O'Neill M, Hewitt J, Smith A, Azhari H and Dawson J. Post Stroke Diabetes Management: A Qualitative Study. (AA-19-1029). The Article manuscripts is submitted at Oxford University Press Age and Ageing Journal for publication.

List of Presentations

Chapter 2

1. Azhari H, Haig C, Macisaac R and Dawson J. Thiazolidinediones and risk of bone fractures: a systematic review and meta-analysis of randomised controlled trials. Oral presentation at the Scottish Society of Physicians the 59th Annual Meeting, Inverness 2017. Abstract published in the Scottish Medical Journal.

2. Azhari H, Haig C, Macisaac R and Dawson J. Thiazolidinediones and risk of bone fracture review and meta-analysis of randomised controlled trials. Poster presentation at the 12th UK Stroke Forum conference, Liverpool 2017. Abstract published in the International Journal of Stroke.

3. Azhari H, Haig C, Macisaac R and Dawson J. Pioglitazone and risk of bone fracture review and meta-analysis of randomised controlled trials. Poster presentation at the 113th Association of Physicians of Great Britain and Ireland, Glasgow 2019. Abstract published in the International Journal of Medicine.

4. Azhari H, Haig C, Macisaac R and Dawson J. Pioglitazone and risk of bone fracture review and meta-analysis of randomised controlled trials. Poster presentation at the 5th European Stroke Organisation Conference, Milan, Italy 2019. Abstract published in the European International journal of stroke.

Chapter 3

5. Azhari H, Haig C, Macisaac R and Dawson J. New antidiabetic drugs and risk of stroke: a systematic review and meta-analysis of randomised controlled trials. Poster presentation at the 113th Association of Physicians of Great Britain and Ireland, Glasgow 2019. Abstract published in the International Journal of Medicine.

6. Azhari H, Haig C, Macisaac R and Dawson J. The new antidiabetic therapies for the prevention of stroke risk and mortality. A systematic review and meta-analysis of randomised controlled trials. Oral presentation at the 5th European Stroke Organisation Conference, Milan, Italy 2019. Abstract published in the European International journal of stroke.

Chapter 4

7. Azhari H, Baylan S, Quinn T and Dawson J. Pioglitazone use after stroke. Exploring stroke survivors' views – The PIOSurvey. Poster presentation at the 14th UK Stroke Forum conference. The International Centre Telford 2019. Abstract published in the International Journal of Stroke.

8. Azhari H, Baylan S, Quinn T and Dawson J. Pioglitazone use after stroke. Exploring stroke survivors' views – The PIOSurvey. Poster presentation at the 6th European Stroke Organisation Conference and World Stroke Organization, Vienna, Austria 2020. Abstract published in the European International journal of stroke.

9. Azhari H, Baylan S, Quinn T and Dawson J. Pioglitazone use after stroke. Exploring stroke survivors' views – The PIOSurvey. Poster presentation at the Stroke 2019, Royal College of Physicians and Surgeons. Glasgow 2019.

Chapter 5

10. Azhari H, Hewitt J; Smith A and Dawson J. Exploring the Barriers to Effective Co-morbidity Management Post-Stroke with a Focus on Diabetes – The COMPOSEd study. Patients and clinicians' views: a qualitative focus groups and interviews study. Oral presentation at the 6th European Stroke Organisation Conference and World Stroke Organization, Vienna, Austria 2020. Abstract published in the European International journal of stroke.

Chapter 6

11. Azhari H and Dawson J. Pioglitazone use after stroke. Story of minds, hearts and bones. The Max Perutz science writing award, University of Glasgow 2020. Abstract published in the Medical Research Council insight blog and the website.

12. Azhari H. Novel strategies for secondary stroke prevention exploring the use of pioglitazone therapy (mixed methods study approach). Oral presentation at the U21 Health Sciences Group Doctoral Student Forum. The International Doctoral Student Experience and Transferability of Doctoral training. University of Glasgow 2019.

13. Azhari H. Survive me from a stroke. Oral presentation at the 3 Minute Thesis Competition at the University of Glasgow 2020.

List of Awards

1. The 5th European Stroke Organisation Conference 2019 Young Investigator Research Awards. A travel grants price of €1000 with a free conference registration.
2. The ESO Stroke Summer School course award, Caen, France, 2020.
3. The science of writing masterclass, 2019. Award from the Medical Research Council.
4. Award winner for the best oral presentation at the U21 Health Sciences Group Doctoral Student Forum. The International Doctoral Student Experience and Transferability of Doctoral training. University of Glasgow, 2019.
5. The academic presenter Award from the Saudi Academic Club for Saudi students in UK, representative by the SA Cultural Bureau in London, 2019-2020.
6. Eight Academic Excellence Awards from the Saudi Arabian Cultural Bureau, London, UK, 2015-2020.
7. Distinction Award from Prince Khalid Al-Suad, the Saudi Ambassador to the UK, 2020.

List of Scientific Courses, Workshops, Certificates and Membership

1. Systematic Reviews and Meta-Analyses of Health Research, London School of Hygiene & Tropical Medicine, 2016.
2. Systematic Reviews and Meta-Analyses online course
3. Training course at randomised controlled trials. St John's College, Cambridge and Oxford Universities.
4. Essentials of Clinical Trials, London School of Hygiene & Tropical Medicine, 2020.
5. Become a master of peer review
6. Research data management and how to write a data management plan, 2016.
7. Introduction to SPSS programme, 2016.
8. Introduction to R programme. The UBDC Training programme, 2017.
9. Software Carpentry course at Python and Git workshop, 2017.
10. Introduction and workshop to data visualisation and Tableau, 2017.
11. Introduction to NVivo, 2017.
12. Introduction to EndNote, 2018
13. The UofG LEADS Programme for academic writing, development and critical analyses, 2018−2019.
14. NRS good introduction and update to good clinical practice training course (GCP)
15. Primary care workshop - Stroke prevention: hypertension, AF, TIA and secondary prevention. The 15th UK Stroke Forum, Telford, UK 2019.
16. Misk Fellowship & Traineeship: Future path program with Bloomberg and Fullbridge, UK 2019.
17. The edad program by McKinsey & Company Middle East, UK 2020.
18. How to develop a successful clinical trial in stroke workshop (in collaboration with the ESO Trials Committee). The 5th European Stroke Organisation Conference and World Stroke Organization, Milan, Italy 2020.
19. The ESO Guideline development workshop 2020. The 6th European Stroke Organisation Conference and World Stroke Organization, Vienna, Austria 2020.
20. The European Stroke Organisation (ESO) membership, 2020-2021.
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22. Clinical Observership in the Acute Stroke Unite in the Queen Elizabeth University Hospital, Scotland, UK with Professor Jesse Dawson from June-August 2020.
23. The taster module of neuroimaging and pathophysiology of stroke, University College of London, 2020.
24. The European MSc in Stroke Medicine, Danube University, Krems, Austria, 2020-2022.

Abbreviations

ACS – Acute coronary syndrome

AEs – Adverse events

AHG – Anti-hyperglycaemic agents

Alpha-glycosidase inhibitors – α-glycosidase inhibitors

BBB – Blood brain barrier

BMD – Bone mineral density

CIs – Confidence intervals

CKD-III – Chronic kidney disease stage-III

CVD – Cardiovascular disease

DPP4-Is – Dipeptidyl peptidase-4 inhibitors

DXA – Dual energy x-ray absorptiometry scan

FN – Femoral neck

GLP1-RAs – Glucagon-like peptide-1 receptor agonists

HbA_{1c} – Haemoglobin A_{1c}

HR – Hazard risk

HS – Haemorrhagic stroke

ICH – Intracranial haemorrhage

IGT –Impaired glucose tolerance

IR – Insulin resistance

IS – Ischaemic stroke

LS – Lumbar spine

MACEs – Major adverse cardiovascular events

MCID – Minimal clinically important difference

MedDRA – Medical dictionary for regulatory activities

MeSH – Medical subject heading

MI – Myocardial infarction

MSD – Mean standard difference

OR – Odd risk

PPAR-γ – Peroxisome proliferator-activated receptor gamma

PRISMA – Preferred reporting items for systematic reviews and meta-analysis framework

RCT – Randomised control trial

RD – Risk difference

ROS – Reactive oxygen species

RR – Relative risk

RRR – Relative risk reduction

SAEs – Serious adverse events

SD – Standard deviation

SMD – Standardised mean difference

SGLT2-Is – Sodium-glucose cotransporter-2 inhibitors

T2DM – Type 2 diabetes mellitus

TIA – Transient ischaemic attack

TZDs – Thiazolidinediones

Clinical trials abbreviations

ACCORD – The Action to Control CardiOvascular Risk in Diabetes

ACTIVE-A – Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-A

ACTIVE-W – Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events-W

ACT NOW – Actos Now for the prevention of diabetes

ADOPT – A Diabetes Outcome Progression Trials

ALLHAT – Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ASCOT – Anglo-Scandinavian Cardiac Outcomes Trial

BARI2D – Bypass Angioplasty Revascularization Investigation in type 2 Diabetes

CAPRIE – The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events

CARESS – The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis

CARMELINA – The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin

CAROLINA – The Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes

CHANCE – Clopidogrel in High-Risk Patients with Non-disabling Cerebrovascular Events

DECLARE-TIMI 58 – Multicentre Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events

DIGAMI-1 and 2 – Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 1 and 2

EAFT – European Atrial Fibrillation Trial

ELIXA – Evaluation of Lixisenatide in Acute Coronary Syndrome

EMPA-REG OUTCOME – Empagliflozin Cardiovascular Outcome Event in Type 2 Diabetes Mellitus Patients

ESPRIT – European/Australian Stroke Prevention in Reversible Ischaemic Trial

ESPS-2 – European Stroke Prevention Study-2

EXAMINE – Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

EXSCEL – Exenatide Study of Cardiovascular Event Lowering Trial

HARMONY – Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide

HPS – Heart Protection Study

IRIS – Insulin Resistance Intervention after Stroke

LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

OMNEON – A Study to Assess Cardiovascular Outcomes Following Treatment with Omarigliptin [MK-3102] in Participants with Type 2 Diabetes Mellitus [MK-3102-018]

PERISCOPE – Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation

PIONEER-6 – Peptide Innovation for Early Diabetes Treatment

POINT – Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke

PROactive – PROspective pioglitazone clinical trial in macro-vascular events

PRoFESS – The Prevention Regimen for Effectively Avoiding Second Strokes

RECORD – Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy

REWIND – The Researching Cardiovascular Events with a Weekly Incretin in Diabetes

SAVOR-TIMI-53 – Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction 53

SPARCL – The Stroke Prevention by Aggressive Reduction of Cholesterol

SUSTAIN-6 – Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

TECOS – Trial Evaluating Cardiovascular Outcomes with Sitagliptin

WARSS – The Warfarin and Aspirin Recurrent Strokes Study

WASID – The Warfarin-aspirin Symptomatic Intracranial Disease Study

Abstract

Pioglitazone, an oral thiazolidinedione (TZD), is used in the second- or third-line management of type 2 diabetes mellitus (T2DM). In addition, the Insulin Resistance Intervention after Stroke trial showed that pioglitazone reduced cardiovascular events in people with recent ischaemic stroke or transient ischaemic attacks who were insulin resistant but had no diabetes (relative risk reduction of 24%; 95% confidence interval (CI) 0.62-0.93; *P*=0.007; absolute risk reduction of 3%) versus placebo. Furthermore, with pioglitazone use, about half as many patients went on to develop diabetes. However, the net benefit of pioglitazone has been questioned because, with its use, the fracture rate increased by about a third (29% relative risk (RR); 2 to 5% absolute risk (AR)), many patients suffered substantial weight gain (55% RR; 6% AR) and there was an increase in peripheral oedema (43% RR; 10% AR). This means doctors are unsure about whether they should use pioglitazone. This is a much-discussed topic in the stroke community. This thesis addresses several areas concerning pioglitazone use after stroke. It aims to better characterise the risk of fracture, explore patient and clinician views regarding pioglitazone use and explore whether other new diabetes treatments could be similarly effective in people with strokes.

The fractures, weight gain and peripheral oedema associated with pioglitazone use are important clinical issues. However, fractures are the most concerning. I performed a systematic review and meta-analysis of the fracture risk with TZD drugs following best-practice guidance. A search of the Cochrane Register of Controlled Trials, MEDLINE, EMBASE, the Web of Science and the trial registries (from their inception to Week 36, 2017) was performed. The updated searched was done in Week 10 in 2020. The grey literature was also searched. Published and unpublished studies comparing TZDs with placebo or other anti-hyperglycaemic drugs were included if they reported data on fracture occurrence. The search identified 860 studies. A total of 78 were included in this study as they satisfied the eligibility criteria. Thirty-four included trials had a high risk of bias, eight had unclear risk and 36 low risk. These studies had an overall high-to-moderate GRADE score of evidence. They included 39,568 participants on TZDs and 25,718 on comparators with 1,917 fracture events. The fracture risk was increased with TZDs (RR 1.35; 95% CI 1.24−1.48; *P*<0.00001; I^2=10%) versus controls. In 14 trials comparing pioglitazone versus placebo (13,451 participants; 449 fractures), pioglitazone use increased fractures (RR 1.21; 95% CI 1.01−1.45; *P*=0.04; I^2=32%). Both non-serious (RR 1.25; 95% CI 1.03−1.51; *P*=0.02; I^2=53%) and serious fractures (RR 1.48; 95% CI 1.10−1.98; *P*=0.01; I^2=24%) increased with pioglitazone use. In 13 trials comparing pioglitazone to anti-hyperglycaemic

comparators (11,267 participants; 99 fractures), there was no increase in fracture risk (RR 1.08; 95% CI 0.73−1.59; *P*=0.70; I^2=15%). Fracture risk increases occurred mostly in the spine (RR 2.13; 95% CI 1.28−3.55; *P*=0.004; I^2=66%) and the lower extremities (RR 1.85; 95% CI 1.33−2.56; *P*=0.0002; I^2=0%) with pioglitazone use. Increased risk was more evident in females (RR 1.56; 95% CI 1.20−2.02; *P*=0.0008; I^2=0%) than in males (RR 1.10; 95% CI 0.84−1.43; *P*=0.49; I^2=14%) with pioglitazone use. Pioglitazone use increases fractures, but this finding was mostly driven by studies that compared its use to placebo and by an increase in women. These data may help stroke clinicians decide whether to use pioglitazone in selected patients to guide further post-stroke trials.

There are several new classes of antidiabetic drugs, some of which have been demonstrated to reduce cardiovascular risk. I assessed the effects of these therapies on the incidence of stroke via a systematic review and meta-analysis of stroke outcomes. A systematic search of the Cochrane Register of Controlled Trials, MEDLINE, EMBASE, the Web of Science and trial registries (from their inception to Week 36, 2017) was performed. The updated searched was done in Week 10 in 2020. Published and unpublished trials comparing dipeptidyl peptidase-4 inhibitors (DPP4-Is), glucagon-like peptide-1 receptor agonist (GLP1-RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) to placebo or other anti-hyperglycaemic drugs were included if they reported data on stroke outcomes. The search identified 960 trials. Of these, 256 were included in this study as they satisfied the eligibility criteria. Of these, there were no stroke events were reported in 82 studies and there were 174 trials with at least one event. These included 59,180 people treated with DPP4-Is, 36,069 with GLP1-RAs, 32,816 with SGLT2-Is and 104,570 with comparators. There were 3,914 stroke outcomes. Thirty-two studies had a high risk of bias, 19 an unclear risk and 205 a low risk. These studies had an overall moderate GRADE score of evidence except for fatal stroke with a low-to-very low quality of evidence. The use of DPP4-Is (95 trials, 109,243 participants, 1,431 stroke events) did not reduce the occurrence of stroke (RR 0.93; 95% CI 0.84−1.03; *P*=0.14) for either ischaemic (RR 0.95; 95% CI 0.84−1.07; *P*=0.38) or haemorrhagic (RR 0.68; 95% CI 0.22−2.12; *P*=0.51) events versus placebo or comparator therapies. The use of GLP1-RAs (33 trials, 70,443 participants, 1,637 stroke events) did reduce the occurrence of stroke (0.84; 95% CI 0.77−0.93; *P*=0.0005) and ischaemic events (RR 0.85; 95% CI 0.77−0.94; *P*=0.002) versus placebo but there was no reduction in haemorrhagic stroke rate (RR 0.50; 95% CI 0.09−2.73; *P*=0.42) versus placebo or comparator therapies. The use of SGLT2-Is (46 trials, 52,949 participants, 846 stroke events) did not change the risk of stroke (RR 1.01; 95% CI 0.89−1.16; *P*=0.84) for either ischaemic (RR 1.03; 95% CI 0.89−1.19; *P*=0.68) or haemorrhagic (RR 0.39; 95% CI 0.10−1.58;

P=0.19) events versus placebo or comparator therapies. There was no evidence of a reduction in the risk of fatal stroke with these classes versus placebo or comparator therapies. For all classes, no evidence of statistical heterogeneity, I^2=0.00. The GLP1-RAs may reduce the risk of non-fatal stroke, but there was no evidence of a reduction in stroke rate with the DPP4-1s or SGLT2-Is agents. These findings may help physicians guide treatment of T2DM in people at risk of stroke.

Next, I explored patients' views regarding the use of pioglitazone therapy after stroke in a study called the *PIOSurvey*. We performed a structured survey of stroke survivors registered in the Scottish Health Research Registry. They were given a summary of the evidence for pioglitazone use and side effects (SEs) and asked a series of questions covering the following main themes: 1) whether they would be happy to take pioglitazone, 2) which potential SEs were of most concern, 3) which strategies to mitigate risk were most acceptable and 4) whether they would be willing to take part in further clinical trials. A total of 2,335 electronic invites were sent (714 were read, 145 recipients completed the survey). Of the respondents, 96 (66%) were unlikely/very unlikely to take pioglitazone and only 28 (20%) were likely/very likely to take it. Fractures were a significant concern, as was weight gain. A total of 93 respondents (65%) and 124 respondents (85%)) respectively rated fracture and weight gain as very important/important to them compared to 78 (53%) regarding recurrent stroke and myocardial infarction (MI). A total of 108 (75%) supported further research, five (3%) suggested we should not perform more research or use pioglitazone and 32 (22%) felt we should discuss using pioglitazone with patients now. Stroke patients were concerned regarding pioglitazone SEs, rating these as more important than the risk of stroke or MI recurrence. They would be unlikely to take pioglitazone but support further studies. Further trials to refine the risk/benefit ratio are needed.

I also conducted focus groups to assess the view of patients, caregivers and clinicians regarding the post-stroke management of diabetes ('exploring the barriers to effective Co-morbidity Management POSt-strokE with Diabetes Focus': The *COMPOSEd* study). This study employed a qualitative exploratory design using the grounded theory approach that contributed to our exploration of the use of new treatments for diabetes after stroke and the acceptability of pioglitazone treatment for post-stroke management to minimise its associated SEs and to capture and analyse the barriers to its adoption among primary and secondary stroke care services. Three focus groups were held between February and July 2018 with 19 participants from Glasgow, Scotland and Newport, Wales. Typically, the stroke survivors felt the risk of stroke to be more important than treatment-related SEs

(weight gain and fractures) and seemed more willing to accept these risks rather than further disability. The professionals felt they had gaps in their knowledge regarding new drugs for post-stroke diabetes management. Although stroke patients appeared more willing to accept pioglitazone-induced SEs than a higher risk of stroke, the healthcare professionals were more concerned with the drug-associated SEs. The healthcare professionals were also likely to modify their clinical practice based on standardised recommendations or guidelines. Healthcare professionals suggested exploration of methods to reduce pioglitazone-associated SEs such as better individual selection, dose reduction, professionals' monitoring of early signs of SEs, the early use of preventive management for fractures and lifestyle measures and modification. Healthcare providers believed these might allow more treatment adherence and confidence in their decision making and practice. These findings suggest that further research is needed before widespread use of pioglitazone and that education is needed regarding use of new diabetes drugs.

In summary, pioglitazone use is associated with a clinically significant relative risk of fractures, but such fracture events may not all be serious and thus may not be as important as preventing further recurrence of stroke or MI. However, the review was limited by the reliability of the included studies, which used a broad range of fracture definitions and included little data on people with previous strokes. Compared with DPP4-1s and SGLT2-Is, the GLP1-RAs use may reduce non-fatal stroke risk. Although some views expressed in the focus groups differed from the survey findings, both patients and clinicians are reluctant to use pioglitazone to prevent recurrent stroke at present. Some guidelines suggest, however, that pioglitazone use can be considered in individual patients after considering the risks and benefits. Further research is needed to optimise the risk/benefit ratio of this use and to identify people for whom the benefits would be largest and the risk acceptable. The findings of this thesis confirm the need for such studies.

Chapter 1 Pioglitazone as a Novel Therapeutic Target for Risk of Stroke, Transient Ischaemic Attacks and Myocardial Infarction, a Secondary Preventive Therapy

1.1 The epidemiology of stroke and stroke recurrence

Stroke is the second most common cause of death worldwide after ischaemic heart disease (IHD), with 6.7 million deaths occurring annually. [1] [2] Over the period of 1990−2016, data from a systematic analysis done for the Global Burden of Disease Study [3] showed that there were 13.7 million (95% uncertainty intervals (UI) 12.7−14.7) new stroke cases and 80.1 million prevalent stroke cases (95% UI 74.1−86.3) globally. The study also estimated that the number of deaths due to haemorrhagic stroke (2.8 million [95% UI 2.7−2.9]) was slightly higher than the number due to ischaemic stroke (2.7 million [95% UI 2.6−2.8]). There were 116.4 million (95% UI 111.4−121.4) disability-adjusted life-years due to stroke. In particular, a higher number of prevalent stroke cases was reported for women (41.1 million [95% UI 38.0−44.3]) than men (39.0 million [95% UI 36.1−42.1]). This inequality across gender may be partly explained by women's longer lifespan and by fact that hypertension, atrial fibrillation (AF) and diabetes mellitus could be mediated risk factors for stroke development and occur more frequently in women. [4] However, further differences between women and men in vascular biology, immunity, lifestyle factors, societal roles, hormonal profiles and the risks related to pregnancy, the postpartum state and menopause seem to contribute. [4] [5]

The sharp rise in behavioural and metabolic risk factors has contributed to increased risk of stroke. Indeed, 90.5% (95% UI 88.5−92.0) of the strokes were attributed to the modifiable atherosclerotic risk factors analysed, 74.2% (95% UI 70.7−76.7) to behavioural factors (such as low physical activity, poor diet and smoking), 72.4% (95% UI 70.2−73.5) to clusters of metabolic factors (such as high body mass index, high systolic blood pressure, high total cholesterol, high fasting plasma glucose and low glomerular filtration rate) and 28.1% (95% UI 25.3−30.9) to environmental risk factors (such as air pollution and lead exposure). [6] Such factors may count as independent risks for stroke development that vary by the type, underlying aetiology and severity of stroke, [7] which is in line with previous findings about cardiovascular disease (CVD) risk factors. [8] As the global metabolic profiles change, these factors can be expected to increase the prevalence of stroke. In addition, many of these risk factors interact wholly or partly with other risk factors. The remaining stroke burden is attributed to unmeasured or unknown risk factors, genetic factors, or the effect of gene/environment interactions. [6] Controlling the combined effect of behavioural and metabolic risk factor clusters therefore would likely avert more than three-quarters of the stroke burden globally.

There are also clear disparities in the rate of strokes between different race and ethnic groups. In many regions around the globe, most stroke morbidity and mortality occur in low- and middle-income countries and among non-Western, [9] non-Caucasian groups such as the Black, Japanese, Chinese and South Asian populations. [10] In the European region, over the next 25 years, the annual incidence of stroke is projected to rise by over 30%. [11] In the United Kingdom (UK), almost two-thirds of stroke survivors in England, Wales and Northern Ireland leave the hospital with a disability. [12] Approximately 40,000 people in the UK individuals die each year due to stroke. [13] Of the survivors, over one half suffer a broad spectrum of disabilities. [14] These range from no disability (42%) to partial disabilities (22%) to full dependency (12%). For those with no disability or minimal disabilities, a major source of subsequent mortality and morbidity is recurrent stroke and myocardial infarction (MI). The Stroke Association's 'State of the Nation: stroke statistics' note that over 25% of stroke patients in the UK will experience recurrent transient ischaemic attacks (TIAs) or strokes within five years of their initial event and 12% will have cardiac events, with 20% dying from one of these conditions. [15] It is of interest that those who have suffered stroke have a higher risk of recurrent stroke than patients who have suffered cardiac events such as MIs. These results suggest that primary prevention strategies are not widely implemented or not effective. Given the overall increase in the stroke burden, it is crucial to implement prevention strategies that target stroke-related risk factors.

1.1.1 Ischaemic brain injury and the burden of stroke

During ischaemic stroke, the disruption in blood supply induces anaerobic metabolism of glucose that results in lactic acid accumulation. Secondary hypo-metabolism occurs due to the direct toxic effect of acidosis on mitochondrial functioning, leading to a vicious circle of worsening acidosis and increasing anaerobic metabolism. [16] [17] As a result, a dysfunction in the sodium-potassium transporters occurs, causing cytotoxic oedema and intracellular osmolarity. Increased calcium concentration occurs and, ultimately, enhanced release of intracellular glutamate. [18] The integrity of the blood-brain barrier (BBB) is compromised, which increases the risk of haemorrhagic transformation of the infarcted tissue from vasogenic oedema if the blood components enter the interstitial space. If the blood flow is swiftly restored, some of the ischaemic penumbral tissue may be saved. [19] It is estimated that up to two million neurons are lost every minute if reperfusion treatment is delayed. [20]

1.1.2 Glycaemia and risk of stroke

Diabetes represents one of the most common chronic diseases worldwide. It is estimated that, by 2040, the disease will affect 415 million people worldwide, of whom approximately one-half will remain undiagnosed. It is estimated that up to 549,000 people with diabetes in the UK remain undiagnosed, representing 6% of the total percentage of people with diabetes, including the undiagnosed, or one in every 16 people with diabetes. [21]

Diabetes is a metabolic disorder characterised by high blood glucose levels caused by insulin insensitivity or lack of insulin production. Type-1 diabetes mellitus is associated with a partial or complete lack of insulin that results from autoimmune-mediated pancreatic β-cell destruction. Type-2 diabetes mellitus (T2DM) is characterised by differing degrees of imbalance in insulin secretions, hepatic glucose production, varying degrees of insulin resistance and moderate-to-severe pancreatic β-cell apoptosis. [22] The occurrence of insulin resistance is also related to CVD risk factors such as obesity, hyperglycaemia, dyslipidaemia and hypertension. [23]

Hyperglycaemia occurs commonly in acute stroke (in around one-third of cases). [24] This may reflect pre-existing but unrecognised diabetes or an acute stress response to stroke. Stress hyperglycaemia is defined as a random glucose of >11.1 mmol/l or fasting glucose of >6.9 mmol/l during hospitalisation without evidence of previous diabetes. [25] Therefore, during acute stroke, it can be challenging to distinguish between diabetes and admission hyperglycaemia. Most studies describe such associations in the majority of people after stroke, in as many as two-thirds of individuals across all clinical subtypes of ischaemic stroke and in at least 50% of lacunar strokes, [26] [27] with an incidence of around 27% in nondiabetic individuals and 78% in people with diabetes in the first 48 to 88 hours after stroke. [28] Hyperglycaemia is associated with poor outcomes, but it is uncertain whether the link between poor stroke outcomes and glycaemia reflect a causal association. Following cerebral ischaemia, the body's acute stress response is a key factor in development of hyperglycaemia. However, it could be argued that the hyperglycaemia is just an epiphenomenon that indirectly reflects stroke severity and the patient's condition. In such a setting, an elevated HbA_{1c}, the glycosylated form of haemoglobin, of ≥6.5% may help identify those with true previously undiagnosed diabetes. [29]

The mechanistic pathways of hyperglycaemia-mediated brain damage are complex. In preclinical and clinical studies, hyperglycaemia is associated with a higher incidence of

brain oedema, [24] a larger infarct volume size, [30] haemorrhagic transformation and neuronal cell death. [31] Over time, reactive oxygen species accumulate, [32] increasing the intracellular acidification, [33] causing inflammatory response induction, [34] impairing recanalisation and causing BBB disruption, [35] leading to reperfusion injury and thus contributes to brain axonal degradation. [36] [37] Hence, it is debatable whether the stress hyperglycaemic states in acute stroke patients is critical to manage or not. [38]

Several treatment approaches, including lifestyle modifications and pharmacological interventions, are used treat diabetes and its complications. Glucose-lowering drugs include biguanides, thiazolidinediones (TZDs), incretins such as (dipeptidyl peptidase-4 inhibitors (DPP4-Is) and glucagon-like peptide-1 receptor agonist (GLP1-RAs), sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) and α-glucosidase inhibitors), insulin and insulin secretagogues (sulfonylureas). [39] Pioglitazone, a class of the TZDs family, is currently approved as a second- or third-line potent insulin sensitizer used either as monotherapy or as a combination therapy with metformin or sulfonylureas. It has been shown to improve the glucose tolerance of people with poorly controlled diabetes and to delay the onset of diabetes in people at risk. [39] In combination therapy with metformin, sulfonylurea or insulin, pioglitazone use at high dose of 30 mg/day appeared to be effective in the control for blood glucose and lipids in patients with poorly controlled T2DM and was more effective than a dose of 15 mg/day. [40]

The relationship between the risk of stroke and glycaemic control remains unclear. Hypoglycaemia is associated with a twofold increase in the hospitalisation rate for stroke, [41] which suggests that glucose-lowering drugs that induce hypoglycaemia might be increasing the hospitalisation rate. Pioglitazone is recommended as an added treatment for people with T2DM for whom the higher priority is avoiding hypoglycaemia. [42] This drug does not increase hypoglycaemia compared to placebo [43] whether it was used alone or as an add-on to existing anti-hyperglycaemic regimens. However, a small percentage of patients may experience this unintended effect when pioglitazone is combined with sulfonylurea or insulin. [44] If desired, this effect can be avoided by prophylactically titrating the dosage, [45] reducing the insulin dose, [46] [47] or, in some patients, stopping insulin entirely. [48] [49] However, no standardized meta-analysis or head-to-head clinical trials have been done to compare these medications in terms of their longer-term beneficial or deleterious impacts on people with stroke.

In T2DM, the HbA_{1c} level is mainly used as an indicator of glycaemic control and to assess a treatment's efficacy. When pioglitazone is used as a sole therapy for diabetes, it is moderately effective in combating hyperglycaemia. At a maximal dose of up to 45 mg, it has been shown to lower the HbA_{1c} by an average of 1 to 1.5%. In patients with secondary failure to metformin and/or sulfonylureas [50] therapy, pioglitazone decreases the HbA_{1c} value to a statistically durable degree that is clinically equivalent to the effect of metformin, [51] sulfonylurea, [52] or insulin without causing hypoglycaemia, as what is observed with sulfonylureas or insulin. [50] It has also been shown to reduce cardiovascular events in people with diabetes or insulin resistance. [53]

1.1.2.1 Insulin resistance and risk of stroke

Impaired insulin sensitivity, which includes insulin resistance and impaired fasting glucose, has emerged as a potential important risk factor for CVD. In particular, this sensitivity has been associated with adverse sequelae that increase risk for coronary artery disease [54] and carotid atherosclerosis. [55] [56] [57] [58] [59] The impaired insulin sensitivity phenotype affects over 90% of people with T2DM but is likewise highly prevalent (a rate of more than 50%) among individuals without diabetes who have had recent cerebrovascular disease. [60] [61] [62] [63] [64] To put these figures in context, such prevalence is particularly high among younger individuals with central obesity, lacunar stroke aetiology or physical disability. [54]

Neither the aetiology nor pathophysiology for insulin resistance is completely understood. However, an associated systematic consequence of hyperinsulinemia, hyperglycaemia, dyslipidaemia, [65] inflammation, increased platelet reactivity, endothelial dysfunction, [66] hypertension, [67] hypercoagulability [68] and the stimulation of cells involved in atherogenesis. [69] It could be that the impacts of direct sympathetic activation, [70] endothelial dysfunction [71] and hypertension [67] increase risk for lacunar infarction of small vessels disease more often than other types of ischaemic stroke. It is estimated that the average hazard risk of stroke increases by 1.12 (95% CI 0.91−1.39) in people without diabetes and 1.17 (95% CI 1.09−1.25) in people with T2DM with each 1% increase in the HbA_{1c} level. [72] Therefore, it is critical to investigate whether a treatment with therapeutic implications for improving insulin sensitivity can reduce the risk for subsequent TIA, stroke and/or heart disease.

The overall evidence of a beneficial effect of intensive glycaemic control on CVD and stroke risk is limited. Recent reviews [73] suggest that insulin therapy produced a

statistically significant 11% reduction in major adverse cardiovascular events (MACEs) (HR 0.89; 95% CI 0.82−0.97) without any evidence of alleviating the hazard risk of stroke (0.96; 95% CI 0.83−1.10) versus conventional glucose lowering. In contrast, some very recent large clinical CVD trials found clinically significant evidence of the lessening of the hazard risk of MACEs with thiazolidinediones pioglitazone (0.86; 95% CI 0.76−0.96) and stroke (0.81; 95% CI 0.66−1.00) and with GLP1-RAs therapies (0.87; 95% CI 0.83−0.92) and (0.82; 95% CI 0.74−0.91). However, there was no consistent evidence for the benefits of other new antidiabetics—for example, DPP4-Is therapies had a neutral impact on MACEs (0.99; 95% CI 0.91−1.07) and stroke (1.02; 95% CI 0.88−1.18), and SGLT2-Is therapies evidently decreased the hazard risk of MACEs (0.89; 95% CI 0.83−0.95) but had neutral impacts on stroke (1.00; 95% CI 0.88−1.13).

The impact of the putative application of conventional glucose lowering therapies and new antidiabetic agents following stroke is uncertain. The results of large clinical CVD trials would be considered disappointing by those who hoped that the epidemiological relationship of glycated haemoglobin or plasma glucose levels to MACEs and cardiovascular mortality would translate to reductions in stroke risk with these drugs. But the effect on stroke recurrence specifically has not been studied. The effect of metformin, an insulin-sensitising treatment that improves end-organ sensitivity to insulin effects, in mitigating the risk of further MACEs and stroke and meta-analysis of clinical trials in acute stroke at best remains limited. It also presently offers no strong association of stroke reduction in people with T2DM. [74]

1.2 The peroxisome proliferator-activated receptors (PPARs) in the cardiovascular system

To date, the family of peroxisome proliferator-activated receptor (PPARs) agonist consists of three highly homologous subtypes of the nuclear hormone receptors that are encoded by separated genes. These subtypes are members of the steroid receptor superfamily. [75] The first member is PPAR-α, which was originally discovered as a mediator by which several xenobiotic drugs cause peroxisome proliferation in the liver. This receptor is predominantly expressed in the heart, vascular wall, liver, muscle, stomach mucosa, kidney and brown adipose tissues. [76] Its primary observed function is to improve plasma lipids via increasing levels of high-density lipoprotein (HDL) cholesterol, apolipoprotein-A1 and fatty-acid oxidation pathways by decreasing very high low-density lipoprotein (LDL) levels.

[77] The second member is the PPAR-β receptor, which is also known as PPAR-δ. This receptor is most highly expressed in the brain, skin and adipose tissues. However, preclinical experimental studies revealed that, when the PPAR-β/δ receptor is ablated (PPAR-δ null mice), and the tissues displayed alterations such as diminished myelination and delayed wound healing in animal models that result in a rare type of skin cancer. [78] For this reason, the discussion here will mainly be limited to other subtypes. The third member is the PPAR-γ receptor, which is most often expressed in the heart, vascular endothelium, macrophage, pancreatic β-cells, [79] [80] spleen, large intestine and white and brown adipose tissues. [81] [82] The gene encoding PPAR-γ is located on chromosome 3 at position 3p25. [83] This receptor's key functions, when it is further activated, are to control blood glucose and lower the circulatory levels of fatty acid and the pro-inflammatory markers and mediators of atherosclerosis. [84] Alternative splicing of PPAR-γ produces three major isoforms: PPAR-γ1, which is expressed in virtually all tissues; PPAR-γ2, which is restricted to adipose tissue; and PPAR-γ3, which is expressed in macrophages and white adipose tissue. [85] Isoforms 1 and 3 are somewhat similar, while 2 differs due to its ligand-independent region at the N-terminus. [86] [87] However, this isoform is predominantly expressed in bone marrow mesenchymal stem cells (MBSCs) and play a critical role in the differentiation of pre-adipocytes into adipocytes and their lineage determination. [88]

In summary, the defined functions for all PPARs have mainly been their ability to regulate energy balance, with PPAR-α being involved in β-oxidation pathways [89] and PPAR-γ in the differentiation of adipocytes. The PPARs agonist can be activated by a vast number of compounds, including synthetic drugs, clofibrate therapies (synthetic ligands for PPAR-α), [90] and antidiabetic TZD classes (synthetic ligands for PPAR-γ). Therefore, there has been a great deal of interest in whether these therapies may open the possibility that modulating PPAR-α/γ isoforms can lead to novel therapeutic targets that have implications for metabolic disorders that predispose individuals to inflammatory diseases as atherosclerosis, including dyslipidaemia, insulin resistance and diabetes mellitus, [91] for the prevention of ischaemic stroke. [92]

1.2.1 Pioglitazone as a novel therapeutic target for risk of stroke, transient ischaemic attack and myocardial infarction as a secondary preventive therapy

The evidence supporting the use of diabetes treatments following recent strokes or TIAs has been enhanced by the Insulin Resistance Intervention after Stroke (IRIS) Trial, [93] which demonstrated that pioglitazone use in people with insulin resistance is beneficial. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study [94] also showed that pioglitazone use reduces the recurrent stroke rate in people with diabetes at high risk for MACEs.

In the PROactive study, [94] the central hypothesis was that pioglitazone would lead to a reduction in cardiovascular events compared to placebo. In people with T2DM and at risk for MACEs (*n*=5,238; mean age 61.8 years and HbA_{1c} >7.5%), pioglitazone used for 34.5 months had a nonsignificant benefit on the primary composite endpoints of all-cause mortality, non-fatal MI (including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical interventions of the coronary or leg arteries and above-ankle amputations (odd ratio (OR) 0.90; 95% CI 0.80−1.02; *P*=0.095). However, in post-hoc analyses of PROactive patients with (*n*=984) and without (*n*=4,254) previous strokes, pioglitazone showed a significant beneficial reduction in the non-fatal and fatal stroke incidence (hazard ratio (HR) 0.53; 95% CI 0.34−0.85; *P*=0.0085) and CVD mortality risk for stroke or MI (HR 0.72; 95% CI 0.52−1.0; *P*=0.0467). [95] [96] These data suggest that pioglitazone may reduce the risk of stroke recurrence in people at high risk for MACEs and stroke.

1.2.1.1 The Insulin Resistance Intervention after Stroke (IRIS) study

The IRIS study [93] proved that use of pioglitazone following ischaemic stroke or TIA, within the past six months, in people with insulin resistance (*n*=3,876 and mean age 63.5 years, of which 65% male) reduces non-fatal and fatal MI and strokes (HR 0.76; 95% CI 0.62−0.93; *P*=0.007) versus placebo. At five years after the occurrence of a stroke or TIA, it is estimated that for, every 100 patients treated with pioglitazone with ischaemic stroke and insulin resistance, three fewer individuals would suffer recurrent strokes or MIs. A relative risk reduction (RRR) of 24%, absolute risk reduction of 3% and 36 number need to treat with pioglitazone versus placebo. This benefit is comparable to other primary and secondary preventive drugs such as aspirin [97] and statins. [98] [99]

In the IRIS study, [100] a total of 155 strokes occurred in 138 participants in the pioglitazone group versus 222 strokes in 181 participants in the placebo group. At trial entry, stroke subtype was classified as cardioembolic for 284 participants (7.4%), large vessels atherosclerosis for 1007 participants (26.0%), lacunar for 1146 participants (29.6%) and uncertain type for 1336 participants (34.5%). After five years of follow-up period, pioglitazone use reduced the risk any stroke (8.0% pioglitazone versus 10.7% placebo; HR 0.75; 95% CI 0.60−0.94; *P*=0.01) and ischaemic stroke (7.1% pioglitazone versus 9.9% placebo; HR 0.72; 95% CI 0.57−0.91; *P*=0.005). A subgroup analysis defined by previous strokes type and subtype revealed a potential clinical reduction in lacunar infarctions of the small vessels by 54% (HR 0.46; 95% CI 0.22−0.93; *P*=0.03) along with a trend toward reduced risk for cardio-embolic stroke by 29% (HR 0.71; 95% CI 0.38−1.32; *P*=0.27) and atherosclerotic large vessel disease events by 41% (HR 0.59; 95% CI 0.33−1.04; *P*=0.07).

In the IRIS study [100] at entry, 3375 (87%) of the total participants had an index event of stroke with minor residual impairment (defined as an acute stroke event ≤ 180 days at entry of the study) and 483 (13%) had TIA. After five years of follow-up period, pioglitazone use reduced the risk for ischaemic stroke (7.8% pioglitazone versus 11.3% placebo; HR 0.70; 95% CI, 0.55–0.88; *P*=0.003) and TIAs (9.9% pioglitazone versus 6.8% placebo; HR 1.40; 95% CI 0.71−2.73; *P*=0.33). The majority of IRIS trial participants were on antiplatelets (3567 participants (92.2%)), anticoagulants (441 participants (11.4%)) and statins (3186 participants (82.5%)) at trial entry. For these patients, there was no evidence of increased risk of haemorrhagic stroke (HR 1.00; 95% CI 0.50–2.00; *P*=1.00), including subarachnoid and nontraumatic cerebral bleeds after a five-year follow-up. Such outcomes have been associated with other primary and secondary preventive therapies such as aspirin [101] and warfarin. [102]

A meta-analysis of people with insulin resistance and T2DM also suggests pioglitazone use may reduce the rates of further ischaemic stroke. A meta-analysis of nine randomised controlled trials (RCTs) (three trials in people with pre-diabetes or insulin resistance and six trials in people with T2DM, *n*=12,026) that had a mean follow-up duration of 2.7 years concluded that pioglitazone use was associated with an RRR of 19% in the incidence of recurrent stroke and an RRR of 22% in further development of MACEs. These findings included mortality rate reductions of fatal and non-fatal events versus placebo and active comparator drugs for T2DM treatment of 23% and 17%, respectively. [53] I note here,

however, that some may argue that most of the trials reviewed in this meta-analysis (the IRIS study was one exception) were not designed to examine stroke risk as a primary endpoint.

1.2.2 Pioglitazone therapy and risk of stroke

In stroke, the biological efficacy of pioglitazone, PPAR-γ agonist, has been attributed to various effects. In a meta-analysis [103] of nine preclinical studies using rodent models (n=939), pioglitazone was found to have a beneficial neuro-protective action against global or focal cerebral ischaemic injury. In brain parenchyma, pioglitazone reduced the infarct volume size with an improvement of neurological functional outcomes (standardised mean difference 1.50 and 1.20; P<0.00001; respectively), independent of time, dose, or experimental modelling (permanent or transient). Experimental stroke studies [92] demonstrated that pioglitazone decreases cyclooxygenase-2 expression and various inflammatory driven-neurotoxic mediators such as nitric oxide, tumour necrotic factor-α and interleukin-6, which appear following the activation of microglia / macrophages during neuronal inflammation and oxidative injury. Pioglitazone use also promotes neovascularisation and vasomotor reactivity [104] by the induction of adhesive molecules and antioxidant enzymes to prevent further neuronal apoptosis. [92] These data support the idea that PPAR-γ activation may have some neuroprotection benefits in stroke and be an effective secondary preventive intervention for early ischaemic brain injury.

The primary pharmacological action of TZDs is to act as a key regulator of energy metabolism in adipose tissue and to inhibit hepatic gluconeogenesis. [105] [106] These drugs exert their antidiabetic effect via the activation of PPAR-γ, which plays an important role in free fatty acid (FFA) metabolism through a range of direct and indirect mechanisms. In nondiabetics and diabetics, it is hypothesised that pioglitazone spares other insulin-sensitive tissues such as the liver, pancreatic β-cells and skeletal muscle from the harmful metabolic effect of high concentrations of FFA, lipotoxicity [107] or glucotoxicity via promoting their uptake and storage in adipose tissues, [105] [106] consequently increasing the tissues mass and keeping fat where it belongs. This is the so-called fatty-acid-steal direct hypothesis. [108] [109] Since PPAR-γ receptors are more abundant in adipose tissue than in any other tissue, they up-regulate genes involved in adipogenesis and fatty acid metabolism to enhance the plasma adiponectin secretion. [106] [110] The adiponectin activates hepatic and muscle adenosine 5′ monophosphate-activated protein kinase, stimulates fatty acid oxidation and inhibits excessive hepatic synthesis. [107] This activity is described by the liver insulin-sensitization indirect theory. [111] [112]

1.2.2.1 Pioglitazone therapy effects on markers of stroke and cardiovascular disease

Since the pathogenesis of atherosclerosis is a multifactorial pathway involving dyslipidaemia, lipoprotein oxidation and inflammatory cell interactions, it is possible that pioglitazone may have profound effects on the CVD markers. [113] [114] In the vascular endothelium, pioglitazone regulates the expression of endothelial nitric oxide synthase, [115] limiting the T-cell expression of pro-inflammatory cytokine regulators and the subclinical biomarkers of systemic inflammation such as C-reactive protein, interferon-γ and interleukin-2. [112] The drug attenuates atherosclerotic plaque hyperplasia [116] and reduces the progression of atheroma. [52] [117] These changes are independent of changes in glycaemia or the lipid profile and occur in nondiabetics and diabetics. [118] However, such observations cannot be simply translated clinically as class effects of TZD since rosiglitazone, another antidiabetic agent in this family, has been linked to an increase in the MI rate in several meta-analyses. [119] [120]

1.2.2.2 Myocardial infarction risk

After the publication of clinical trials linking rosiglitazone to increased CVD morbidity and mortality, the study of the cardiovascular effects of diabetes drugs has been crucial. In contrast to rosiglitazone, the data for pioglitazone treatments show a significant reduction in cardiac events. In a Nissen meta-analysis [119] of 42 RCTs involving people with or without diabetes (n=46,456; mean age 56 years and baseline HbA_{1c} 8.5%), rosiglitazone use for 24 to 52 weeks was associated with increased MI risk (OR 1.43; 95% CI 1.03−1.98; P=0.03). There was also a borderline nonsignificant trend toward an increasing mortality rate related to CVD (OR 1.64; 95% CI 0.98−2.74; P=0.06) versus controls. Following that, however, an updated rosiglitazone meta-analysis [121] that stratified these results by comparator drug and duration of exposure showed nonsignificant trends toward increasing MI (OR 1.59; 95% CI 0.88−2.88; 11 RCTs) and cardiovascular mortality risk (OR 1.44; 95% CI 0.76−2.73; 9 RCTs) with rosiglitazone use versus placebo after more than a year of follow-up (OR 1.22; 95% CI 0.96−1.57; 14 RCTs). Of note here is the fact that the cardiovascular results for the studies included in these meta-analyses did not always relate to their primary or secondary endpoints. Also, of note is that these studies were conducted over a relatively short follow-up period. Given the heterogeneous nature of the included study population and low event rates in many trials, meta-analyses of these mixed post-marketing phase IV cardiovascular

outcome trials and pre-marketing trials from phase II and III development programs is insensitive for assessing cardiovascular risk.

To evaluate the incidence of greater CVD risk among people with diabetes, a retrospective data analysis was performed by the rosiglitazone manufacturer, GlaxoSmithKline. Compared to patients treated with other anti-hyperglycaemic agents, people with T2DM treated with rosiglitazone had a significant OR increase for MIs developing 1.31% (95% CI 1.01−1.70). [122] As a result, the US Food and Drug Administration (FDA) assessed relevant data and concluded that rosiglitazone use was associated with greater risk of OR for all ischaemic events of 1.40% (95% CI 1.1−1.8; *P*=0.00). [123] In contrast, in a nested case-control analysis of a retrospective cohort study of people with T2DM (*n*=159,026 with mean age ≥66 years), pioglitazone use was not associated with an excess rate of acute MI (RR 0.73; 95% CI 0.40−1.36; *P*=0.33) whereas with rosiglitazone use was (RR 1.76; 95% CI 1.27−2.44; *P*<0.001). [124]

The largest and longest rosiglitazone study is the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD). [125] This study designed to complete a comprehensive assessment of rosiglitazone cardiovascular safety as primary and secondary endpoints versus metformin and sulfonylurea. However, the open-label design of this trial might lead to bias. It is important to acknowledge there were more patients in the rosiglitazone group on statin therapy (55.2% compared to 46.0% in active comparators), and such imbalances in background therapy may influence these cardiovascular outcomes. However, the overall MACEs point to estimates of 95% CIs in the RECORD trial are consistent with the FDA guidance for cardiovascular safety that, with minimal effect, remained at less than 1.3. [126] [127] These data however suggest that there are important differences exist between these TZD sub-classes.

Pioglitazone has more favourable cardioprotective effects than placebo and other antidiabetic therapies. In a PROactive subgroup analysis, [128] in people with a previous MI within ≥6 months (*n*=2,445), pioglitazone use reduced the RR of fatal and non-fatal events by 28% (95% CI 0.52−0.99), hospitalisation admission rates by 22% (95% CI 0.63−0.96), acute MI risk or cardiac revascularisation by 15% (95% CI 0.75−0.98) and ACS (*n*=715) by 37% (95% CI 0.41−0.97). Of note, a meta-analysis [129] evaluated the CVD incidence in 19 RCTs among diverse peoples with T2DM (*n*=16,390; mean age 58 years). The results showed that for four months to 3.5 years, pioglitazone use was associated with a significant HR reduction of 18% (95% CI 0.72−0.94) for the primary composite endpoints of death,

non-fatal MI and stroke against comparators. The direction and magnitude of the positive effect is homogeneous across studies of various comparators, durations and populations with or without established CVD risk factors. These data however indicate that the two glitazones may have different impacts on the risk of CVD development.

In the PROactive study, [94] pioglitazone use decreased triglyceride (TG) levels by 11.4% and increased the median HDL by 19% from the baseline versus a 1.8% increase in TGs and a 10.1% increase in HDL with placebo (P<0.0001 for both). On the potentially harmful side, there was also an increase in the median LDL levels of 7.2% with pioglitazone use versus a 4.9% increase with placebo (P=0.003). Compared to placebo, these effects were accompanied by a significant improvement in the LDL to HDL ratio of −9.5% with pioglitazone use versus −4.2% with placebo (P<0.0001). This finding of an overall neutral-to-positive effect on the lipid variables correlates with the finding that, despite the occasionally seen increase in LDL with pioglitazone, the drug has never been associated with an increase in the hard-clinical endpoints of MI. Although both glitazones can increase LDL levels, there are pivotal differences in their lipoprotein metabolism. Pioglitazone has more off-target effects on PPAR-α activation and acts as a partial agonist, whereas rosiglitazone is a pure agonist [130] and is a more potent ligand agonist for PPAR-α than pioglitazone. [131] [132]

The mechanism through which rosiglitazone provokes the incidence of MI and/or cardiovascular mortality remains unclear. One potential contributing factor, however, is the paradoxical effect of both TZDs on the serum lipids profile. In a meta-analysis of 23 RCTs (T2DM and dyslipidaemia patients n=8,000; mean age 57 years), [133] rosiglitazone was found to have a significant undesirable increase of five to 10% in LDL (15 mg/dL or 0.39 mmol/L) and total cholesterol (21 mg/dL or 0.54 mmol/L) along with a neutral effect on TG levels (1.1 mg/dL or 0.12 mmol/L) and a lesser increase in the HDL values (2.7 mg/dL or 0.07 mmol/L). In contrast, pioglitazone used as a monotherapy or in combination with another anti-hyperglycaemic was shown to have a neutral effect on LDL (0.4 mg/dL or 0.01 mmol/L) and total cholesterol while it decreased the TG level by 15% (40 mg/dL or 0.45 mmol/L) and increased the HDL values by >10% (4.6 mg/dL or 0.12 mmol/L). Since diabetes to a certain degree is characterised by a raised TG level, a low plasma HDL and near normal LDL values with an increased number of dense and small LDL particles, these differences may be important. [134] [135] [136] [137] Such quantitative contributions with pioglitazone use lead to a reduction to a very low LDL and the overall LDL particle

concentration with a robust ability to elevate the LDL particle size and produce a more pronounced shift from dense, small atherogenic type A patterns to more buoyant, less atherogenic type B patterns. [138] [139]

1.2.3 Therapeutic target of pioglitazone therapy and its impacts on bone fracture, body weight, peripheral oedema and heart failure risks

1.2.3.1 Bone fracture

In diabetes, bone loss was not a major concern for most clinicians until the PROactive and IRIS studies noticed an overall incidence of fractures that, while relatively low, was significantly higher with pioglitazone use. The first signal that pioglitazone may increase fractures emerged in 2005 in the PROactive study [94] as an unexpected finding from a post-hoc analysis of non-adjudicated spontaneous adverse events (AEs). In 2016, the IRIS study [93] revealed that general fracture rates were increased by approximately one-third (29% RR and 2 to 5% AR) with pioglitazone use. At five years post-stroke, the estimated cumulative incidence of fractures was 3% with pioglitazone versus 2% with placebo with absolute risk difference (ARD) of 1%.

Fracture risk may be more frequent in women with pioglitazone use. In the PROactive study, the females had a significantly higher rate of fractures per 100 patient years with pioglitazone use versus placebo (1.0 versus 0.5), while the males had no differences in this rate among pioglitazone and placebo (0.6 versus 0.7). [140] [94] Whereas, in the IRIS study, [141] both genders were observed to have an increased fracture risk. The excess risk in women was calculated to be 3.7% with pioglitazone use versus 2.8% against placebo per 100 patient years. For men, fracture risk was 2.3% with pioglitazone use versus 1.3% against placebo per 100 patient years. Hence, the observed increased fractures risk with pioglitazone use post-stroke in IRIS study was in line to other previous studies that examined fractures risk after stroke. [142] [143] [144] [145] While the higher hazard risk for both genders in IRIS differs from the PROactive findings, neither study was designed to exclude chance as an explanation for the observed differences in fracture risk across genders or to evaluate that risk according to menopausal status or for people with or without osteoporosis.

The skeletal location of fractures with pioglitazone use is an interesting issue. In the PROactive [140] and Pioglitazone Effect on Regression of Intravascular Sonographic

Coronary Obstruction Prospective Evaluation (PERISCOPE) [146] studies, but not in Actos Now for the prevention of diabetes (ACT NOW) [113] trial, the fracture AEs were limited to females, who recorded more peripheral fractures. In the IRIS study, [141] distal upper- and lower-limb fractures were more evident in females and males than in the PROactive study. [140] The IRIS study [141] also found that spinal fracture in men was increased (HR 9.12; 95% CI 2.13−39.16) compared to women (HR 1.24; 95% CI 0.63−2.43) with pioglitazone use. This was striking but based only on 21 men and had a very wide CI. However, after the adjustment of the IRIS participants baseline fracture features that varied the risk did not change any of these sex-related findings. The IRIS study [141] was conducted with a relatively middle-aged population (mean = 63±11) in which spinal and hip fractures were rare. [147] Given the different biomechanics, microarchitecture, structural integrity and composition of the spine compared to other skeletal areas, the spine is more susceptible to microdamage. [148] [149] [150] [151] However, such IRIS findings give credence and brings light to concerns about axial fractures in men with pioglitazone use post-stroke. It is possible that other hidden confounding factors rather than sex may associate to increase the risk of peripheral and/or spinal fractures.

Stroke patients already have a higher risk of falls [152] and bone loss, [142] [143] so they may be at an even higher risk of fracture with pioglitazone use. It is important to acknowledge here that in the IRIS study the fracture results were for people with insulin resistance post-stroke. Whereas all patients enrolled in the PROactive study [94] who had T2DM and evidence of pre-existing CVD, they were a heterogeneous population of which only 18.8% had a previously documented occurrence of stroke. It is noteworthy these events occurred in groups of particularly ill patients and that neither study measured or monitored the duration or frequency of fracture-related stroke disabilities, the time to healing or the recovery rates. This failure might have led to an overestimation of the fracture risk in those stroke survivors.

It is crucial to highlight that the literature provides plenty of preclinical, [153] [154] epidemiological [155] [156] and clinical trials [157] [158] data that likely confirms the association between TZDs and fractures. Such evidence suggest that an increased risk for fractures in those treated with TZDs became apparent during the second year of treatment and in women. [159] However, most of the reviewed clinical data predict the fracture risk with rosiglitazone and pioglitazone use in people with T2DM without identifying subgroup differences in the severity of fractures event in people with stroke according to the longevity

of drugs exposure. [160] [161] However, the fracture incidence has not been examined as a primary or secondary endpoint in these studies so although it seems likely fracture risk is increased it cannot be certain it is not a chance finding.

The mechanism(s) associated with TZDs that prompt bone loss are obscure and complicated. [162] [153] PPAR-γ signalling regulates the fate of pluripotent BMSCs. Experimental models suggest this signalling causes an imbalance that affects bone remodelling. The BMSCs are able to differentiate into diverse cell lines (adipocytes, chondrocytes, myoblasts and osteoblasts) and TZDs may increase their differentiation into adipocytes [163] [164] [165] [166] and thus cause fat to accumulate in the bone marrow. [167] [168] This may be due to a negative effect on the expression of a gene indispensable for osteoblast development Runt-related transcription factor-2. [163] The differential effects on PPAR-γ isoforms may also be important. PPAR-γ1 promotes bone resorption (osteoclasts), [169] whereas PPAR-γ2 [167] suppresses bone formation (osteoblasts) through affecting the lineage allocation of bone cells, increasing their ability to break down bone and induce osteocytes apoptosis. [170] [171] [172] An imbalance between osteoblast and adipocyte formation [170] [171] [173] may be the core cause of bone impairments.

Likewise, TZDs play a role in oestrogenic metabolism by pointing to the functional crosstalk between oestrogen and the PPAR-γ receptors. In bone marrow, osteoblasts form a competition between these receptors for a common coactivator steroid receptor coactivator-2. [174] The canonical wingless-type integration site family (WNT) is an important regulatory pathway in osteogenic differentiation and activation. In oestrogen deficient murine cells in vitro and in humans, osteoblasts decrease the activity of the WNT and insulin growth factor-1 pathways [173] by enhancing sclerostin up-regulation [175] and inhibiting the aromatase expression in adipose stromal cells, [176] resulting in a further osteocytes apoptosis. Cellular mechanism studies suggest that TZDs inhibit oestrogen and testosterone synthesis and removes the insulin-induced stimulation of oestrogen and testosterone production while stimulating progesterone production. [165] [177] [178] This effect may contribute to the observed degree of bone loss. Therefore, females and older people may more vulnerable to fractures if they are treated with TZD therapies.

In different murine models, TZD pioglitazone has detrimental effects on trabecular bone. [179] In hematopoietic lineage cells, mice deficient in the PPAR-γ expression c-fos protein, an essential mediator of osteoclastogenesis, [180] [181] are less sensitive to TZD-induced bone loss than the controlled mice. [180] Therefore, if we block the pathway of c-

fos protein, it may prevent the aggravated risk of fracture with these therapies. This is a novelty area for further study. However, in humans, pioglitazone stimulates adipocyte precursor formation that reduces the BMSCs commitment to differentiating to osteoblasts [179] and thereby reduces the osteocalcin [182] and procollagen type-I N-terminal propeptide (P1NP) in postmenopausal women, [183] which decreases bone formation. Bone microarchitecture and mass marker analyses show a decrease in the volume and bone formation that increase in the resorption rates. In men, however, TZD therapies reduce osteoprotegerin [184] with a significant increase in sclerostin and the β-C-terminal telopeptide of type-I collagen along with a modest rise in P1NP levels, [185] which are a bone resorption markers.

1.2.3.2 Weight gain

In the IRIS study, [93] insulin resistance individuals on pioglitazone had an RR of 52% and an AR of 6% for weight gain. Extreme weight change differences were observed across groups, with a 2.6 kg (0.4 stone) mean gain associated with pioglitazone use versus a 0.5 kg mean loss with placebo (P<0.001). At four years from trial entry, most individuals in the pioglitazone group (52.2%) gained over 4.5 kg (0.7 stone). A smaller group (11.4%) gained over 13.6 kg (2 stone). However, it is notable that, despite such gains, overall there were fewer cardiovascular events.

The weight gain associated with pioglitazone use may not be a bad outcome. In the PROactive study, [140] with pioglitazone the average weight gain was 3.8 kg (after 30 months or at the final visit from the baseline) versus 0.6 kg weight loss with placebo, in which majority of this gain occurred during the first 15 months. However, as a result only 0.8% of the PROactive patients in the pioglitazone group discontinue the study medication permanently compared with 0.2% in the placebo group. In the PROactive, [186] however, the mortality rates were lower with increased weight gain in people with diabetes at risk for MACEs (per 1% gain; OR 0.96; 95% CI 0.92-1.00; P=0.037). In fact, the increased weight with pioglitazone use was accompanied by a favourable metabolic impact on body fat redistribution. For years, the association between improved insulin sensitivity among TZD therapies, weight gain and fat redistribution [109] from visceral to subcutaneous tissues has been recognized. Subcutaneous adipose tissue mass is more abundant in PPAR-γ receptors in which visceral and overall adiposity may be unchanged or decreased despite weight gain. [109] [187] In subcutaneous fat, pioglitazone use selectively increase adipogenesis, which may not be detrimental compared to similar processes in visceral fat. [109] [188] [189] Even

if weight gain occurs, pioglitazone use may decrease the mean hip-to-waist circumference ratio. [190]

In people with T2DM treated with pioglitazone, the relationship between body weight and the HbA_{1C} level, a diabetes progression mediator, is U-shaped. A weight gain of 2 to 3 kg occurs for every 1% decrease in the HbA_{1c} level during monotherapy [191] [192] [193] and the concomitant use of metformin, [190] [194] sulfonylureas [195] or insulin. [196] Pioglitazone has been chiefly attributed to an expansion of subcutaneous fat deposits and partly to peripheral oedema. This may explain the paradoxical result seen in the PROactive study [186] in which pioglitazone use may have promote fluid retention, caused oedema and increased the plasma volume that leads to excess weight.

1.2.3.3 Fluid retention (peripheral oedema)

A retrospective analysis of unadjudicated events in the PROactive study [197] noted that oedema in the absence of heart failure (HF) was reported more with pioglitazone use (563 participants (21.6%) on pioglitazone versus 341 participants (13%) on placebo; $P<0.0001$). A subgroup of patients experienced water retention and plasma volume expansion that led to lower extremity (ankle) swelling (11% with pioglitazone). However, these incidents were not adjudicated or defined as pre-specified endpoints in the PROactive study.

Peripheral oedema is not correlated with an increased HF mortality risk with pioglitazone use. In the IRIS study, [93] insulin resistance individuals on pioglitazone developed more significant oedema defined as a self-reported new or worse swelling of the feet or lower legs (691 participants (35.6%) on pioglitazone versus 483 participants (24.9%) on placebo; $P<0.001$) but there was no increase in the risk of HF development. In a post-hoc analysis of the IRIS study, [198] however, weight gain, peripheral oedema or shortness of breath did not predict the risk of HF hospitalisation in people at high risk for stroke.

Peripheral oedema and weight gain have been associated with increased HF incidence in selective cases. In a systematic review [40] of the clinical effectiveness of pioglitazone of RCTs, an increase in peripheral oedema occurrence of 4% to 6% that was reported with pioglitazone use against an increase with placebo or other anti-hyperglycaemic therapies of 1% to 2%. The increase for pioglitazone use was worse when its use was accompanied by intensive glucose therapy as with insulin drug. However, the underlying

mechanisms of peripheral oedema and weight gain due to fluid retention are not likely to be correlated.

Although the definitive reasons for pioglitazone use to prompt peripheral oedema have not been clarified, some possible explanations have been proposed. Experimental studies in mice models [199] [200] found that pioglitazone activates the PPAR-γ receptors, which are the sensors responsible for plasma volume control, in the inner medullary collecting duct of kidney nephrons at the distal convoluted tubules. This activation increases the reabsorption of sodium through the epithelial channel. [200] In humans, the overactivation of these receptors increases the plasma aldosterone and renin levels, [201] which decreases the renal excretion of sodium and alters the intestinal ion transport. Therefore, there is a tendency for fluid accumulation and plasma volume expansion owing to the renal sodium retention. [201] This unfortunately increases the development of HF if the sodium levels are unchecked. [129]

1.2.3.4 Heart failure

People with diabetes are at double risk for HF development. [202] It is estimated that in people with T2DM the prevalence of HF is 12% to 20% and that the risk is five times higher in diabetic women and 2.4 times higher in diabetic men than for general population. [203] Risk factors such as being female, being older, having a longer duration of diabetes, hypertension, IHD and increased serum creatinine are independent risk factor for HF development. [204]

Pioglitazone use increased the incidence of HF development however did not translate to increased subsequent morbidity or mortality rate. In the PROactive study, [197] pioglitazone increased HF hospital admissions by 5.7% versus 4.1% with placebo in those at risk for MACEs (P=0.007). However, mortality due to HF was similar (25 cases of 0.96% with pioglitazone; 22 cases of 0.84% with placebo; P=0.639). However, in a subgroup stratification of those with a previous cerebrovascular disease (n=984), [96] a nonsignificant trend increase was seen in 31 cases of 6.4% with pioglitazone use versus 20 cases of 4% with placebo; P=0.0946. Regardless of their differences in the percentage of HF development, the mortality rate related to HF did not increase or differ across groups (1%; P=0.63). However, no provisions for this finding were made in their statistical analysis plan as these uncertain events were not pre-specified or independently adjudicated in the trial.

In the IRIS study, [198] patients on pioglitazone reported dyspnoea more frequently. In total, 151 patients with 187 events in the pioglitazone group and 144 patients with 180 events in the placebo group were reported as potential episodes of HF, of which respectively 67 patients and 66 patients confirmed HF. Across the trial baseline risk of HF, the effect of pioglitazone use on the HF development did not differ significantly—the HRs was 1.03% (95% CI 0.61−1.73) for those at low risk, 1.10% (95% CI 0.56−2.15) for those at moderate risk and 1.08% (95% CI 0.58−2.01) for those at high risk. At five years of follow-up period, the risk of HF development was low and was not differ across groups of randomisation (74 cases of 4.1% with pioglitazone; 71 cases of 4.2% with placebo) or for HF hospitalisation (51 patients of 2.9% with pioglitazone; 42 patients of 2.3% with placebo) with a mortality-related event rate of <1% in each group. However, pioglitazone use posed a more significant hazard risk of HF development in those with previous MIs (31.4% pioglitazone; 25.7% placebo) versus those without previous MIs (2.7% pioglitazone; 2.4% placebo) (P<0.0001). Indeed, at five years, such risk did not differ across groups (4.1% pioglitazone; 4.2% placebo) and in fact protected them, diminishing their HRs of MI, stroke or serious hospitalisation by 22% (95% CI 0.68−0.93; P=0.007). It is likely that strategies such as excluding those people at risk because of prior HF development at trial entry and titrating the therapeutic dose of pioglitazone carefully minimised the HR risk of HF development.

In the IRIS study, [198] the pioglitazone dose was adjustable, with a mean of 29±17 mg versus 33±15 mg placebo. According to the participants' intention-to-treat analysis, 7% of pioglitazone doses were reduced in those without HF risk and 13% of participants were discontinued from the study drug versus 3% and 5% for the placebo, respectively. The number of patients lost was parallel across groups and similar to previous stroke studies. [205] [206] [207] Indeed, the evidence showed that pioglitazone has not been recognized as a trigger for cardiotoxicity effect on the ventricular contractile function or structure. [208] It is possible that, in people with insulin resistance and stroke, the development of HF is prompted predominantly by the occurrence of MI, which in fact is reduced with pioglitazone use. It seems to be that pioglitazone had no ongoing direct effect on those excluded participants in which induced peripheral oedema or fluid retention perhaps did not sustain after pioglitazone dose modification or discontinuation.

In a meta-analysis of RCTs involving people with T2DM (n=16,390), serious HF was increased with pioglitazone use (2.3% against 1.8% controls; P=0.002). [129] The mechanism for this may be fluid retention without echocardiographic evidence of diastolic

or systolic dysfunction of left ventricle (LV), as suggested by the secondary data analysis from the RECORD and A Diabetes Outcome Progression Trials (ADOPT) studies of rosiglitazone. [209] [210] In hypertensive patients (*n*=30), though, pioglitazone use may enhance the diastolic dysfunction of the LV without mass regression [211] in people with diabetes. [212] Experimental research has shown that TZD use modestly elevates brain natriuretic peptide levels, which may increase LV wall stress and in turn aggravate HF risk. However, there was no dysfunctional echography evidence of infarction. [213] [214] Given the clinical impacts of pioglitazone on LV surrogate markers, studies have not been performed on people with stroke.

It should be noted that other oral hypoglycaemic drugs have been associated with increased HF risk. In a study using data from the UK general practice research database of people with T2DM (*n*=91,521), [215] a monotherapy with first or second-generation sulfonylurea was associated with a significant increased rate (24% to 61%) for all-cause mortality and an unfavourable excess risk for HF development with the second generation of 18% to 30%. In contrast, pioglitazone use significantly reduced all-cause mortality by 31% to 39%. However, given the possibility of confounding by indication or residual confounding, differences in prognostic factors across groups cannot be excluded. This raises concerns as to whether sulfonylureas should remain an acceptable first-line add-on to metformin in the management of people with T2DM. [216]

From the evidence that has emerged, pioglitazone-induced peripheral oedema is not associated with a higher mortality rate of HF, at least at present with the available data from the PROactive and IRIS clinical studies. There is also no evidence of a corresponding excess in cardiovascular mortality from previous meta-analyses of pioglitazone clinical trials. [129] [217] Concerning the weight gain risk-benefit profile, pioglitazone use may be a reasonable choice in appropriately selected patients with no diabetes (HbA_{1c} 5.8%), although the generalisability of the IRIS study results for patients after acute attacks of ACS or MI are uncertain. Whether the clinical impacts of pioglitazone on susceptible individuals however would translate into longevity effects on the disease progression of macro- or micro-vascular diabetic cardiomyopathy needs to be clarified.

1.3 The guidelines for the managements of vascular risk factors in ischaemic stroke/transient ischaemic attack

Current strategies for preventing cardiovascular events after stroke include antiplatelet and anticoagulant therapy, hypertension and lipid management and carotid endarterectomy. Despite these effective strategies, [218] people who have had strokes still experience recurrent cardio- and neurovascular events. Although significant declines in CVD mortality have been achieved in the UK, CVD remains a considerable burden in terms of health and costs. [14] Therefore, primary and secondary preventive measures, as well as novel therapeutic approaches, are urgently needed to further reduce this burden.

1.3.1 Antiplatelet therapies

In the UK, there are four licensed antiplatelet therapies for preventing stroke recurrence: aspirin, clopidogrel, dipyridamole and their combination. However, aspirin is the only licensed strategy for the primary prevention of stroke.

Aspirin (acetylsalicylic acid) is effective in minimising the incidence of first cardiovascular events [219] [220] [221] [222] [223] in the distinctly healthy population at adverse risk for CVD. An RCT meta-analysis of these clinical trials [224] including over 55,000 patients, of whom 25% were women, found an RRR of 32% for first MI (95% CI 0.59−0.79) and of 15% (95% CI 0.73−0.93) for any important vascular event, along with a nonsignificant RRR of 6% (95% CI 0.87−1.29) for non-fatal stroke. Individual trial subgroup analyses suggest a benefit for females, although it did not reach statistical significance in one group. [221] [223] Subsequently, a sex-specific meta-analysis [225] of primary preventive trials that included 95,456 individuals, of whom 50% were women, confirmed a reduction in cardiovascular events and stroke of 17% (95% CI 0.7−0.97) but no reduction in the cardiovascular mortality or MI rate. Although men reduced their MI risk of 32% (95% CI 0.54−0.86), however, without a significant reduction in the stroke rate of 13% (95% CI 0.96−1.33). Indeed, there is no clear evidence to support an alternative antiplatelet strategy in the primary prevention setting.

Aspirin is the most commonly prescribed agent in the immediate period following stroke for secondary prevention. [226] [227] It prevents up to one-fifth of recurrent strokes [228] compared to placebo [226] [229] and had a 15% to 22% composite endpoint of

vascular death, non-fatal MI and stroke for doses of 300 or 1200 mg/day. [230] However, aspirin use is associated with bleeding AEs. Low-dose aspirin use increases the RR of major bleeding about 70% (95% CI 1.41−2.08) but had a modest increase in ARs. It is estimated that 769 patients need to be treated to cause one additional episode of bleeding annually. That risk is mainly due to major gastrointestinal bleeding (RR 2.07; 95% CI 1.61−2.66; AR 0.12%) and intracranial bleeding (RR 1.65; 95% CI 1.06−5.99; AR 0.03%). [101] Such an increased in the bleeding AEs associated with aspirin is that in the platelets, aspirin inhibits the constitutive enzyme cyclooxygenase-1 and prevents their further aggregation, thereby lessening their production of thromboxane A2 and prostaglandins, which causes irreversible acetylation. This inhibitory effect will last for the lifespan of the platelet, which makes them, given their lack of nuclei, unable to synthesise that enzyme. Therefore, to maintain aspirin efficacy and minimize such AEs, the US FDA approved aspirin use in the range of 50 to 325 mg/day. [231]

In terms of stroke prevention, dipyridamole or clopidogrel use is not superior to aspirin. For stroke secondary prevention, dipyridamole is superior to placebo but not regarding MI or vascular death recurrence. This drug may have a similar efficacy to aspirin but without a proven preventive benefit in MI. [232] [233] This efficacy was associated perhaps with a significant withdrawal rate due to headache AEs, the incidence of which may be reduced by gradually increasing its dose. [234] [235] Although clopidogrel was linked to a small reduction of 8.7% with the primary composite of MI, ischaemic stroke or vascular death but had a significant difference of 0.51% versus aspirin (P=0.043). This appears to be driven by an effect in those with peripheral vascular disease of 23.8% (P=0.0028) without an observed difference with MI or stroke subgroups in those with recent strokes (RRRs 7.3%; 95% CI 5.7−18.7), as shown by the results from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) in patients with symptomatic CVD (n=19,195). [236]

In the primary prevention of stroke, the early use of aspirin and clopidogrel is more beneficial than using aspirin alone. In a recent secondary analysis of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) and Clopidogrel in High-Risk Patients with Non-disabling Cerebrovascular Events (CHANCE) trials, a combination of aspirin and clopidogrel is beneficial for early stroke prevention of high-risk TIA or acute minor ischaemic stroke. The POINT trial [237] involving 4,881 patients, shows that dual therapy was more beneficial to reduce the rate of major ischaemic events in the first 21 days

(HR 0.65; 95% CI 0.50–0.85; *P*=0.0015) than in comparison to 22 to 90 days (HR 1.38; 95% CI 0.81–2.35; *P*=0.24). When such results considered with the results of the CHANCE trial, [238] involving 5,170 patients, similar beneficial effects observed with the early use of aspirin and clopidogrel therapy within 21 days (HR 0.78; 95% CI 0.65–0.93; *P*=0.006) without increased in the risk of severe or moderate haemorrhage (seven patients (0.3%) in the clopidogrel and aspirin group and nine patients (0.4%) in the aspirin group; *P*=0.44). These findings suggest that limiting the early use of clopidogrel with aspirin dual combination to 21 days may maximise the benefit and risk after high risk TIA or acute minor ischaemic stroke for a duration of one year of follow-up.

In the secondary prevention of stroke, the dual use of aspirin and clopidogrel is no more effective than using either alone. In a pooled meta-analysis [239] of five trials of aspirin and clopidogrel or aspirin use for stroke prevention involving 24,084 patients, of which most had previous cerebrovascular disease, a dual therapy had a significant RRR in the incidence of all-cause stroke of 31% (95% CI 0.59−0.82) for the short term and 16% (95% CI 0.72−0.98) for the long term use. Thus, their effects seem to be more apparent for a shortened period. These combinations could be a preferable choice to prevent strokes in populations with previous stroke, TIAs and among those at higher risk for stroke. However, such combination doubles the risk of life-threatening bleeding episodes in both the long and short term (*P*=0.04 and *P*<0.05, respectively). In those with ≥50% symptomatic atherosclerosis, those allocated to early dual combinations (*n*=107) showed fewer micro-embolic signals and a seven-day RRR of 39.8% (95% CI 13.8−50) without bleeding complication. These results are from the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) trial. [240] These findings highlighted how those with acute stroke, TIAs and large vessel stenosis may benefit from these treatments, as might those with recent symptomatic large diseased vessels.

In the secondary prevention of stroke and serious vascular events, aspirin and dipyridamole are superior to placebo [241] and more effective than aspirin alone. In a meta-analysis [242] of six RCTs involving 7,648 people with minor strokes and TIAs, this combination affords a more significant RRR in stroke of 23% (95% CI 0.67−0.89) and composite endpoints of stroke, MI and all vascular mortality of 15% (95% CI 0.76−0.94). However, an immediate-release form of dipyridamole showed a nonsignificant RRR of 17% (95% CI 0.59−1.15) for stroke. The European/Australian Stroke Prevention in Reversible Ischaemic Trial (ESPRIT) [243] involving 2,739 patients and the European Stroke

Prevention Study-2 (ESPS-2) [232] involving 3,299 patients found a slight reduction of ischaemic stroke with the combination of aspirin and dipyridamole. Compared to aspirin, in contrast, the use of an extended-release form shows a 24% (95% CI 0.65−0.89) reduction in stroke and a composite of stroke, MI and all vascular mortality of 18% (95% CI 0.73−0.92). Such benefits with the extended-release form of dipyridamole reflect its anti-inflammatory and non-platelet-mediated pharmacological benefits and inhibitions of platelet reuptake phosphodiesterase-5 activity and adenosine. [242] That reduction and a lack of increasing bleeding complications is curious and surprising. [244] Their combination with clopidogrel showed no HR differences for recurrent strokes (9% following added agents versus 8.8% with clopidogrel). These data are from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study of 20,332 people with acute stroke. [245]

The evidence suggests that aspirin should be recommended for the primary prevention of non-cardioembolic cerebral ischaemia in women. For men, most evidence suggests this use produces a significant reduction in MI risks. For stroke recurrence, the sole preventive therapy of aspirin, clopidogrel and dipyridamole appears to be of similar efficacious advantage, although clopidogrel monotherapy may be slightly superior to aspirin monotherapy. Adding aspirin to clopidogrel poses unacceptable risks for little gain except in certain high-risk subgroups. Their combination is not routinely recommended for ischaemic stroke or TIAs due to the increased risk of bleeding in longer time of follow-up period. Aspirin plus extended-release dipyridamole has been proven superior to aspirin alone, but recent data suggest this strategy offers a similar yield to clopidogrel monotherapy, which is better tolerated. At present, therefore, the aspirin and dipyridamole combination are a reasonable strategy to employ as a first line. Either aspirin or preferably clopidogrel should be considered for patients intolerant to dipyridamole. However, the selection of these therapies should be individualized on the basis of patients' comorbidity and of cost while weighing the risk-benefit ratios of the combinations.

1.3.2 Anticoagulant therapies

The major cause of cardioembolic stroke is AF, which is the most common heart rhythm disturbance observed in the UK [246]. AF confers approximately a fivefold risk of stroke. [247] [248] [249] During the first 14 days of AF, the risk of stroke recurrence is especially high. [250] [251] [252] The most widely used anticoagulant until recently was warfarin, which inhibits the synthesis of the vitamin K dependent clotting factors II, VII, IX and X.

In primary stroke prevention, warfarin is hugely effective in cases of valvular AF. The pooled analysis from major placebo-controlled trials unveiled a highly beneficial RRR of 68% for ischaemic stroke, [253] the occurrence of which in absolute terms fell from 4.5% to 1.4% per annum with warfarin use. The maximum benefit of warfarin requires the international normalised ratio (INR) to be above 2. [254] [255] The recommended INR range is 2 to 3. A meta-analysis [256] of 29 trials (*n*=28,044 participants; mean age 71 years; mean follow-up 1.5 years) found that a judicious use of antithrombotic therapy minimizes the risk of stroke by two-thirds but had absolute increases in major extracranial haemorrhage of ≤0.3% annually. Compared to the controls, the risk of stroke was reduced with warfarin (six RCTs; 2,900 participants) by 64% (95% CI 49%−74%) and with antiplatelets (8 RCTs; 4,876 participants) by 22% (95% CI 6%−35%). The adjusted-dose of warfarin was more efficacious than antiplatelets (12 RCTs; 12 963 participants) with an RRR of 39% (95% CI 22%−52%). It is clear that antiplatelet drugs are an inferior strategy compared to warfarin.

In the secondary preventive setting, warfarin is highly effective for stroke recurrence of cardiac origin. In the European Atrial Fibrillation Trial (EAFT) [255] with warfarin, the annual rate of stroke, MI, systemic embolism or vascular death was 8% versus 15% with placebo (HR 0.60; 95% CI 0.41−0.87). The rate of vascular events (RR 0.89; 95% CI 0.81−0.98) and the risk of stroke (RR 0.72; 95% CI 0.62−0.83) were significantly lower with clopidogrel and aspirin dual therapy versus placebo for AF patients who were deemed unsuitable for anticoagulants in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A) study. [257] However, the major haemorrhagic rate was increased with this combination from 1.3% to 2% (RR 1.57; 95% CI 1.29−1.92).

There are several direct oral anticoagulants (DOACs) that can be used as alternative agents. These include direct thrombin inhibitors (dabigatran) [258] and factor Xa inhibitors (apixaban, edoxaban and rivaroxaban). [259] In patients with AF, DOAC therapies are at least as good as warfarin for preventing stroke. In a network meta-analysis [102] of 16 RCTs of 96,826 patients, all DOACs were more effective than antiplatelet therapy, halving the composite of stroke. Compared to warfarin, apixaban and dabigatran 150 mg were superior (OR 0.82; 95% CI 0.69−0.97) and reducing the risk of all strokes (OR 0.65; 95% CI 0.52−0.82). However, only dabigatran 150 mg was more effective in reducing the ischaemic event of stroke (OR 0.76; 95% CI 0.59−0.99) than warfarin. Rivaroxaban was superior to dabigatran 110 mg at reducing the MI risk (OR 0.67; 95% CI 0.45−0.99). For risk of major bleeding, aspirin (OR 0.77; 95% CI 0.61−0.98), apixaban (OR 0.71; 95% CI 0.62−0.81),

low-dose of edoxaban (OR 0.48; 95% CI 0.41−0.56), high-dose of edoxaban (OR 0.8; 95% CI 0.71−0.91) and dabigatran 110 mg (OR 0.82; 95% CI 0.71−0.94) produced less risk of major bleeding compared to warfarin and placebo. However, apixaban (OR 0.89; 95% CI 0.8−0.98) and low dose of edoxaban (OR 0.87; 95% CI 0.78−0.96) offered mortality advantages over warfarin and aspirin. The risk of intracranial haemorrhage (ICH) was higher on warfarin and aspirin versus all other DOACs or placebo, whereas the risk of ICH on rivaroxaban was higher than for edoxaban low-dose and dabigatran 110 mg. When patients were switched from DOACs to warfarin after 30 days, though, a double rate of stroke (OR 2.60; 95% CI 1.61−4.18) or major bleeding (OR 2.19; 95% CI 1.42−3.36) were observed. While warfarin remains an effective preventive drug for cardioembolic stroke, the DOACs confer the potential advantages of no requirement for routine dose adjustment or regular monitoring and to be used very early after stroke, yet balancing their benefit for stroke prevention to risk of bleeding is debatable.

In thromboembolic stroke secondary prevention, the timescale of anticoagulant initiation is questionable. In those patients, the early use of heparin is ineffective. [260] [261] [262] Also, whether is it of benefit to people with AF is obscure. [263] In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study [264] (*n*=6,706 patients), the use of dual antiplatelet with aspirin and clopidogrel therapies offered inferior stroke prevention versus warfarin at the cost of a similar burden for risk of bleeding and for safety concerns. However, warfarin was considered safe, with a major bleeding of 1.3% versus 1% in combination or with placebo. Thus, this therapy is generally recommended to be initiated within 14 days in those with AF and stroke, although delay of a week is common. The guidelines suggest that such timing decisions should be individualised [265] but not done too early to prevent a haemorrhagic transformation of infarct following acute ischaemic stroke.

In cases of non-cardioembolic stroke, an anticoagulant is not superior to aspirin for a stroke prevention. [265] About 13% to 26% of all acute ischaemic stroke events are related to non-valvular AF. In the Warfarin and Aspirin Recurrent Strokes Study (WARSS), [266] in 2,206 people with recent ischaemic stroke (within 30 days) without thromboembolic evidence (target INR of 1.4 to 2.8), there were no significant differences in the use of high-dose aspirin 325 mg in its efficacy or death of 16% or in the haemorrhagic rate of 1.5% yearly versus what was observed with warfarin of 17.8% and 2.2%, respectively. In the Warfarin-aspirin Symptomatic Intracranial Disease Study (WASID), [267] in those with

recent stroke and documented 50% to 99% intracranial stenosis (who had no evidence of significant carotid or cardio-embolic disease), there was no beneficial impact from warfarin use alone for stroke recurrence, a finding that was similar across groups (HR 1.04; 95% CI 0.73−1.48). In the ESPRIT study [268] of 1,038 individuals with recent ischaemic stroke, even though ischaemic events were reduced with warfarin (HR 0.73; 95% CI 0.52−1.01) but had significantly worse protection from cardiac events. There was also increased risk of major bleeding (HR 2.56; 95% CI 1.48−4.43) versus high- and low-dose aspirin and a combination with extended-release dipyridamole of 200 mg.

In summary, although DOACs are at least as good as warfarin for preventing stroke, warfarin is the treatment of choice for primary prevention of recurrent stroke with a cardioembolic source and in the AF population whose risk of stroke exceeds the likelihood of bleeding. Aspirin is effective for those deemed unsuitable for anticoagulants and dual therapy with aspirin and clopidogrel leads to a significant fewer strokes rate but increases haemorrhagic risk.

1.3.3 Diabetes mellitus therapies

The National Institute for Health and Care Excellence guidelines for diabetes management suggest metformin as a reasonable initial treatment. However, if hyperglycaemia is not controlled, the addition of a dual therapy, often sulfonylureas, is recommended. [29] Triple therapy with a drug added to metformin is suggested when glycaemic control is no longer sustained or achieved. Despite the widespread use of these drugs, their comparative effects on MACEs mortality outcomes, including MIs or strokes, are heterogeneous. [269] [270] Generally, however, clinical trials have been insufficiently powered to establish the neurovascular preventive impacts of these agents, restricting their ability to inform practice and policy from a single study.

The European [250] and American [250] guidelines for the management of ischaemic stroke and TIAs recommend glycaemic control for primary and secondary prevention of CVD in people with diabetes. [29] [271] [272] The guidelines state that to mitigate the risk of micro- and macro-vascular complications by 25%, the goal for HbA_{1c} should be <7%. [272] [273] However, there are concerns regarding adverse outcomes with more aggressive management. Meanwhile, anti-hyperglycaemic therapy played an important role in reducing the onset of CVD, which was mediated by the gradual accumulation of advance glycation end products. [274] This might subsequently be slowly degraded with intensive glucose

lowering. As a result, the frequent use of insulin, along with the concomitant use of other anti-hyperglycaemic agents, induces the risk of severe hypoglycaemia that coexists with cardiovascular autonomic neuropathy, which is a strong risk factor for sudden death.

Previous trials and their meta-analyses [275] indicate that more rigorous glucose control targeting normal levels of HbA_{1c} in the T2DM population was associated with increased risk of mortality and in fact had no significant impact on MACEs reduction. In other meta-analyses [276] of 13 RCTs involving 58,160 people with T2DM, the intensive glucose lowering therapy was shown to significantly reduce the incidence risk of MACEs of 8% (RR 0.92; 95% CI 0.85−1.00; *P*=0.042) and MI of 10% (RR 0.90 95% CI 0.82−0.98; *P*=0.020) but had a neutral effect on the incidence of stroke of 6% (RR 0.94 95% CI 0.84−1.06; *P*=0.333), congestive HF of 19% (RR 1.19; 95% CI 0.96−1.48; *P*=0.108), cardiac death of 1% (RR 1.00; 95% CI 0.87−1.04; *P*=0.999) and total mortality of 2% (RR 0.98; 95% CI 0.91−1.07; *P*=0.693) compared to conventional drugs. This intensive control greatly reduced HbA_{1c} levels and had direct beneficial impacts for MACEs, which may translate clinically to reducing the risk factor of important comorbidities such as MIs. However, it did not decrease the incidence of further stroke or cardiac death.

Previous clinical trials results on people post-acute MI with or without T2DM were a disappointment but not a cause for despair. In particular, the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial (DIGAMI-1) [277] highlighted that acute treatment with insulin-glucose infusion in people with acute MI (*n*=620 with a follow-up average of 3.4 years), whether or not they were previously known to be diabetic, and a blood glucose concentration of >11 mmol/L had improved their survival rate at one year (8.6% in the infusion group versus 18.0% in the control group; RRR 52%; *P*=0.020). The ARR was 33% with a 28% RRD. This metabolic treatment was estimated to save one life for every nine treated, which is an outcome comparable to thrombolysis therapies.

The DIGAMI-2 [278] trial, in contrast, shown no CVD benefits with the early use of insulin therapy in people with T2DM. The study found that the hospital use of intravenous insulin or community multi-dose subcutaneous insulin versus conventional treatment, in people with T2DM (*n*=1500 with a follow-up of 2 years) with a blood glucose concentration of <11 mmol/L, had a similar absolute mortality rate reduction (around 22% to 23%) at two years across groups. Also, their blood glucose levels were reduced significantly to 9 mmol/L at the study's end. However, these data suggest there were no differences in all-cause mortality between insulin-treated and noninsulin-treated patients regarding non-fatal

reinfarctions and strokes (HR 1.41; 95% CI 0.76−2.62; *P*=0.28 versus HR 1.21; 95% CI 0.62−2.37; *P*=0.58). Despite the use of angiotensin-converting-enzyme inhibitors, beta-blockers, lipid-lowering drugs and aspirin was indeed high. However, whether the reduction in blood glucose levels was related to early intensive insulin use or to the effects on glycaemia control could not be deduced as the levels of admission hyperglycaemia were lower in DIGAMI-2 than in DIGAMI-1 for a relatively small cohort population. This may explain in part the level of absolute CVD mortality reduction post-MI in DIGAMI-1. However, whether such glycaemia lessening could be asserted or translated at the stroke population level remains uncertain as both trials did not predict recurrent stroke rates post-MI in people with stroke with or without T2DM using intensive in-hospital and subcutaneous insulin therapy. This is an area for further research. It therefore seems that the early use of intensive insulin therapy following acute MI does not directly affect the progression of reinfarctions, including strokes.

The relationship between stroke risk and hyperglycaemia has not been clearly affirmed. In a meta-analysis [279] of interventional trials, moderate and/or more intensive glycaemic control therapies were not correlated with any clinically important difference in decreasing stroke risk. Previous meta-analyses [280] that evaluated these treatments as a single factor in the management of people with T2DM may be biased according to multifactorial cardiovascular risk treatments that differ in their characteristics. Whereas, conventional therapies were not adequate to decrease HbA_{1c} values, whether more rigorous glucose control is superior to conventional therapies has not been confirmed to date. [94] [281] [282] In contrast, epidemiological studies [283] have shown a strong association between HbA_{1c} and blood glucose levels and MACE risks. The average hazard risk of IHD increases by 1.18 (95% CI 1.00−1.40), with an increase in the mortality rate related to IHD (HR 1.10; 95% CI 1.04−1.17), stroke (HR 1.17; 95% CI 1.05−1.30) and diabetes (HR 1.32; 95% CI 1.21−1.43) for every 1% change in HbA_{1c} (HR 1.25; 95% CI 1.13−1.38). However, this correlation may be overestimate. Maintaining and achieving optimal glycaemia control without incurring treatment SEs is a challenging task. It is therefore necessary to develop additional effective therapeutic strategies.

1.3.4 Lipid Lowering therapies

The links between coronary heart disease (CHD) and serum cholesterol are well established. However, the debate continues concerning that connection in relation to a therapeutic window in the stroke population. Beyond that expectation, the evidence shows that statins

such as HMG-CoA reductase inhibitors are acceptable as a cholesterol preventive therapy following ischaemic stroke. [265] In a systematic review [284] of 70 studies, of which six were meta-analyses, statins use during acute hospital admissions diminished stroke mortality rates by 41% (95% CI 0.29−0.58) with a good functional outcome for one-third of the patients (95% CI 1.12−1.53). A pre-stroke administration of statins was associated with significant reduction of initial stroke severity by 25% (95% CI 1.05−1.48). It also lowered mortality rates by 42% (95% CI 0.21−0.82) and enhanced functional outcome for half of the patients (95% CI 1.29−1.75). In contrast, a poor functional outcome was seen following withdrawal of statins (95% CI 1.01−3.30). In patients treated with thrombolysis, two-thirds saw an increase in their risk of haemorrhagic transformation (95% CI 1.04−2.56) along with a neurological disability improvement of 44% (95% CI 1.10−1.89). This suggests that statins drugs may enhance collateral circulation and produce better reperfusion after ischaemic stroke but increase the risk of haemorrhagic transformation. This proof of concept however is largely driven by the surrogate imaging marker of observational studies.

One important discovery is the epidemiological link between low serum levels of cholesterol and the incidence of haemorrhagic stroke. This link raises an important probability that statins may increase symptomatic intracerebral haemorrhage. Data from the RCTs diverge, but the pivotal Stroke Prevention by Aggressive Reduction of Cholesterol (SPARCL) trial [98] showed an increase in haemorrhagic stroke rate (HR 1.67; 95% CI 1.09−2.56). Although a meta-analysis [98] found that, when these results are combined with those from the Heart Protection Study (HPS), a significant reduction in the rate of recurrent ischaemic stroke of 20% (HR 0.8; 95% CI 0.7−0.92) with a modest improvement in the patients' overall stroke burden (HR 0.88; 95% CI 0.78−0.99) with statins use. However, the incidence of haemorrhagic transformation with statins use remained high (HR 1.73; 95% CI 1.19−2.5).

The benefit of statins on CHD mortality and morbidity events in those with or without established CVD is an unequivocal benefit. [285] Further compelling data came from the HPS trial, [286] which enrolled 20,536 patients with pre-existing CHD or risk factors. The study showed that simvastatin 40 mg treatment reduced the risk of first stroke by 25% (95% CI 15−34) ≥5 years follow-up and a myopathy rate of one per 10,000 individuals annually. The treatment's effect however was less than expected in terms of its secondary MI protection. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), [287] among those with hypertension, the lipid-lowering assigned arm revealed a similar

magnitude of stroke reduction that was not accompanied by a reduction in cholesterol levels, which was also observed in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). [288] However, on balance, these evidence shows a significant mortality reduction in the incidence of MI and stroke succeeding statins use for those with or without CHD.

Until recently it was uncertain whether statins reduced recurrent stroke rates in those who had experienced previous cerebrovascular events. The SPARCL study [98] of 4,731 patients showed that a high dose of 80 mg atorvastatin led to an RRR of 16% for recurrent ischaemic stroke and most other vascular complications versus placebo. These results were subsequently confirmed in a meta-analysis [289] that also showed a non-fatal stroke reduction from 2.7% to 2.1%. The effect however was less than what would be expected for a secondary prevention of MIs. Approximately 16% of patients in the HPS study [286] had suffered previous strokes, just over half of whom had no documented CHD and that statins use yielded a weakly nonsignificant decline of recurrent stroke of 2% (95% CI 0.79−1.22).

Thus, statins use as a therapeutic intervention is recommended as a preventative strategy in those who have CHD evidence or in those who have experienced ischaemic stroke. [265] [290] For every 10% reduction in LDL cholesterol, statins use appears to afford an RRR of 15.6% (95% CI 6.7−23.6) for stroke. [98] The National Cholesterol Education Program High Blood Cholesterol ATP III (NCEP guidelines and ATP III algorithm) recommend its use for a targeted lipid reduction of <70 mg/dl in those with multiple CVD risk factors and of LDL <100 mg/dl for those with CHD in association with dietary and lifestyle recommendations. The association between serum cholesterol levels and stroke would possibly accord with the connection between CHD and dyslipidaemia, while the heterogeneity of stroke causes identified in the epidemiological studies seems to associate statins with a further haemorrhagic conversion, but this association cannot be assumed. [291] [292] Whether statins should use in those who suffered ICH or who have no other therapeutic indication is unclear. Within the context of secondary CVD prevention, this question raises the possibility that an extended follow-up would reveal the longevity benefits for stroke. An analogous situation exists with statins, that is, clearer results may be produced in trials of longer durations. However, a longer-term follow-up seems to increase the chance risk of rhabdomyolysis. [99]

1.4 Summary

It is clear from major CVD outcomes trials and epidemiological evidence that recurrent strokes and MI are common in stroke survivors, both with and without diabetes. It is therefore obvious that novel preventative therapies are needed. Pioglitazone has been proven to be effective regarding the surrogate markers of diabetes management and CVD prevention. However, fracture risk is raised with pioglitazone use. It remains unclear to what extent this effect on bone health and bone metabolism is a result of the drug class or the complexity of diabetes and stroke. Pioglitazone has been shown to reduce the net clinical points of MACEs, including TIAs, strokes, MIs and HF-related mortality. It also has positive impacts in terms of ameliorating the further progression of diabetes in people who have had strokes. However, when trials of antidiabetic therapies were conducted, the trials investigators attempted to select populations at high risk for CVD that may face considerably more SEs than would be found in routine clinical practice. As with all medicines, pioglitazone has safety issues that should be carefully considered when prescribing it. No validated guidelines have been published for managing people who have had strokes with pioglitazone. According to the updated guidelines, [293] the clinical use of pioglitazone in people with T2DM is acceptable if the benefits outweigh risks. Therefore, it is of great interest to assess whether it can be used after stroke.

1.4.1 What we do not know about pioglitazone therapy

New anti-hyperglycaemic trials were intended to assess cardiovascular safety. However, their findings must be compared cautiously given the differences in their trial designs and patient populations. The clinical practice guidelines concerning the use of pioglitazone as a secondary intervention for the prevention of stroke/TIAs are undecided. When selecting treatment, the recommendations suggest pioglitazone can be considered in individual patients after consideration of desirable and undesirable risks with patient-centred approach for decision-making. However, fractures, weight gain and peripheral oedema are important clinical issues with pioglitazone use, in which making the net benefits risks unclear and debatable.

1.4.2 Aims of PhD

The vision of this thesis is to provide information that will help clinicians decide on whether to use pioglitazone after stroke and to explore the need for and help design further clinical

study. It will examine the recent, most relevant works and explore the future use of pioglitazone to reduce stroke risk using a mixed methods approach. The quantitative studies portion of this thesis summarises all evidence concerning the benefits and risks of pioglitazone compared to placebo and other new or traditional antidiabetic treatments on CVD, focusing on stroke risk, through a detailed, systematic review and meta-analyses of high-quality RCTs. The qualitative studies portion of this thesis explores the barriers to effective stroke prevention after an initial event and survivors' and healthcare professionals' perspectives on pioglitazone use post-stroke. This will identify novel themes for further researches.

Finally, I attempt to do this works in depth to seeking for a further clinical degree with Professor Jesse Dawson and to recruit other PhD students from Saudi Arabia for more collaborative works between the University of Glasgow and Umm Al-Qura.

Chapter 2 Thiazolidinediones and Risk of Bone Fractures. A Systematic Review and Meta-analysis of Randomised Controlled Trials

2.1 Introduction

Pioglitazone, a thiazolidinedione (TZD), may be an effective treatment for preventing recurrent stroke in selected patients. The drug has a high affinity for the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ), [92] which is expressed predominantly in adipose tissue to alter gene transcription and to encode proteins involved in lipid and carbohydrate metabolism. [105] In clinical trials, it has been shown to reduce insulin resistance by 62% in stroke patients. [104] Evidence from the Insulin Resistance Intervention after Stroke (IRIS) trial [93] demonstrated that pioglitazone also reduces non-fatal and fatal myocardial infarction (MI) or stroke in people who have insulin resistance but do not have diabetes and have had strokes or a transient ischaemic attacks (TIAs) in the last six months. However, any health benefits from using the drug were at least partially offset by an increase in fractures (29% relative risk; 2-5% absolute risk). [93] The increased risk of fractures was also indicated in a meta-analysis of 22 clinical trials. [160]

Stroke survivors are at increased risk of falls [152] and fractures. [142] [143] The fracture risk from falls increases two to fourfold in people who have had strokes compared to people who have not had strokes. [294] Indeed, falls occur commonly after strokes. It is estimated that between 14% and 65% of people who have had strokes fall at least once during hospitalisation [295] [296] [297] and that between 37% and 73% fall during the first six months after their hospital discharge. [298] [299] [300] Therefore, the risk of fracture is underestimated post-stroke since fractures are often considered secondary to falls, particularly among those with advancing frailty status. In people with osteoporosis, the mortality risk is increased by about 1.5 times for each standard deviation decrease in bone mineral density (BMD). [301] [302] [303] Although such associations are predominantly due to comorbidities, they may also be attributed to fracture events directly or indirectly. There are many post-stroke issues that increase the risk of falls. [304] Impairments such as functional disability (decreased muscle strength, [305] balance and BMD, [306] a vitamin D deficiency and osteopenia from prolonged immobility [307]) and structural changes (visual or perceptual problems and hemineglect) [295] increase the risk of falls and fractures. Thus, the prevention of strokes and fracture risk is of paramount importance for post-stroke morbidity and mortality reduction.

To assess the net clinical benefit of post-stroke pioglitazone use, we need to better understand fracture risk and its long-term implications. This review aims to summarise the available evidence concerning fracture risk in adults treated with pioglitazone (or other

TZDs), with a particular emphasis on patients with a previous history of stroke. It is hypothesised that pioglitazone (or other TZDs) will be associated with an increased fracture risk in people with or without diabetes who have experienced strokes or TIAs versus placebo or active comparator drugs for type 2 diabetes mellites (T2DM) treatment.

2.2 Methods

The review follows the guidelines of the Preferred Reporting Items for Reviews and Meta-Analysis (PRISMA) framework [308] and the Finding What Works in Healthcare Standards for Reviews [309] to ensure we conducted a high-quality meta-analysis. The protocol was published in the University of York, under the registration of PROSPERO-CRD 42016038242. [310]

2.2.1 Data sources and searches

We searched the Cochrane Central Register of Controlled Trials and Reviews, MEDLINE, EMBASE and the Web of Science for published trials and ClinicalTrials.gov [311] and other registries [312] [313] [314] [315] [316] [317] [318] [319] [320] [321] for unpublished studies from their inception to Week 36 in 2017. The updated searched was done in Week 10 in 2020. The reviews, abstracts and bibliographies of each retrieved article were also reviewed. Search terms included a range of medical subject headings for fractures, TZDs and anti-hyperglycaemic (Appendices 2.1). All studies in all languages were considered.

2.2.2 Study selection

We have included all clinical trials that involved participants aged ≥18 years that reported fractures in people treated with TZDs (compared to placebo and/or other drug treatments for T2DM) either as a monotherapy or in combination with different antidiabetic drug treatments. We reviewed studies that involved any population, that is, people with or without diabetes. All studies were considered regardless of their baseline characteristics, treatment dose, or duration or whether a blinding procedure for the treatment of interest was used.

2.2.3 Data extraction and quality assessment

Data were extracted in a predefined form that involved details on baseline characteristics of enrolled population (the duration of diabetes, HbA_{1c} levels, prior stroke or TIA, age and gender), study design and method, number of patients in treatment and control arms, the

backgrounds of users or non-users of other anti-hyperglycaemic agents and duration of follow-up. When information from the same study was reported in more than one paper, the paper with the most complete data was included. A record of any reasons for exclusion of studies was kept (Supplemental Table 2-1). This was done by H.A. and any issues or difficulties were discussed with J.D.

Each included study was appraised for quality and risk of bias. The risk of bias was assessed according to the judging criteria described in the Cochrane Quality Assessment Tool for assessing bias risk in RCTs. [322] [323] The extracted information was in a predefined form for studies that included details on methods of assessment under six main domains; selection bias, detection bias, performance bias, attrition bias and other potential sources of bias. Each domain was judged to be either 'low risk', 'high risk' or 'unclear', with the last category indicating lack of information or uncertainty. For studies with high risk or unclear, any of the first three bias domains was scored as 'high risk' were considered to have low-quality evidence.

Assessing and grading the certainty of evidence within the meta-analyses was performed using a Recommendation, Assessment, Development and Evaluation (GRADE) approach. [323] [324] The quality would be 'high' where there were several trials with low risk. However, the rating would be lower if there were concerns about the trials' design, [325] imprecision, [326] inconsistency, [327] indirectness [328] and/or publication bias. [329]

2.2.4 Outcomes measures

The primary outcome was the occurrence of any fracture, which was defined according to the standard Medical Dictionary of Regulatory Activities (version.15) [330] for preferred fracture term. The secondary fracture outcomes were fracture subtypes including non-serious and serious events (the latter resulting in hospitalisation, surgery or other procedures), differing mechanisms (non-stress and stress such as repetitive stress or minimal trauma), high energy (e.g., falling from a height higher than standing or motor vehicle accidents), low energy (e.g., falling from a standing height or lower), non-pathological and pathological (e.g., bone disease or osteoporosis), timing (before or after TZD exposure) and anatomical bone sites (spine, hip/pelvis, femur, upper and lower extremities (wrist and ankle)). BMD was also included as a secondary outcome.

2.2.5 Data synthesis (narrative review)

Data were reported in descriptive tables with a detailed narrative. For data synthesis, we categorised comparator anti-hyperglycaemic therapies (mono or in combination) as metformin, sulfonylurea, TZDs, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonist, sodium-glucose contransporter-2 inhibitors, α-glucosidase inhibitors and insulin (Supplemental Table 2-2). To avoid unit-of-analyses errors, the studies with various TZD doses were grouped together to construct a single pairwise comparator. Patients given placebo and anti-hyperglycaemic were grouped together as active comparators.

We decided as a priori to extract data by predefined subgroups such as previous exposure to TZDs. Some trials paralleled >2 interventions groups, which included all members of initial population who were exposed to TZDs (our intervention of interest) during the study. In such cases, we scored them as a high risk of bias and included them in this review but were excluded their fractures data from meta-analyses. A total of 44 studies therefore were included in the meta-analysis (26 as they were open label study design and eight studies were excluded as no fractures were reported).

2.2.6 Statistical analyses

When fracture outcome was reported in ≥2 studies, a meta-analysis was performed to combine these for quantitative evaluation. For dichotomous outcomes, we calculated pooled risk ratio (RR) with 95% CIs and weighted mean differences. For continuous variables, the analysis was based on a statistical summary, which included the outcome mean value of interest (BMD levels), sample size and standard deviation. Fracture outcomes were pooled using a Mantel-Haenszel test. This test allowed for a continuity correction of 0.5 for studies with zero events in any arm. However, both arms with zero-event trials were excluded from such analysis to avoid data distortions.

The meta-analysis was performed for the following outcomes: the incidence risk of fractures including the mechanism and severity of fractures according to different skeletal areas, the participants' gender and the BMD levels. All these events were state to explore the collective impact of our treatment intervention of interest TZD (pioglitazone) on the risk of fracture versus placebo or anti-hyperglycaemic comparators.

Fixed and random-effect models were applied independently. The fixed-effect model assumes the null hypothesis is that each study is estimated from populations with the same effect-size. This model is used when heterogeneity within meta-analyses is absent. However, to further explore the presence of unexplained heterogeneity across subgroups of meta-analyses, we used a random-effect model. [331] [332] This model assumes that different studies estimated from populations with different effect-sizes have related intervention effects. This method is based on an inverse-variance approach that makes adjustments to study weights according to the extent of heterogeneity or the variation among intervention effects.

To assess the percentage of variability across trials, we used inter-study heterogeneity as determined by using a *Q* test that was quantified by the I^2 statistic. A higher score of $I^2 \geq 75\%$ was taken to signify considerable heterogeneity [333] not due to chance. [334] If indicated, Egger linear regression [335] and Begg rank correlation tests [336] were used to appraise for potential reporting bias, which was also visually evaluated with funnel plots. These tests were performed by plotting the total trial inverse sample size (standard error) as an independent variable versus the treatment-effect magnitude of RRs' natural log as a dependent variable. Absent reporting bias, the funnel plot was visualized by a symmetrical inverted funnel.

All tests were two-sided and had the level of statistical significance set at a *P*-value of <0.05. We calculated RR, absolute risk (AR), absolute risk difference (ARD) and the incidence per 100 patient-years. We used Review Manager [337] and GRADEpro GDT [338] software. All analyses were performed by H.A. and reviewed by J.D. and C.H.

2.3 Results

Overall, in our literature review, 860 titles were identified. From these, 301 citations were screened for text retrieval and 105 full-text articles were eligible for review. From these, 78 studies satisfied the eligibility criteria and were included, following the PRISMA checklist [339] (Figure 2-1). These included 39,568 participants treated with TZDs and 25,718 treated with comparators. There were 1,917 fractures within these two groups. The main baseline characteristics of the all included studies is summarized in (Supplemental Table 2-3).

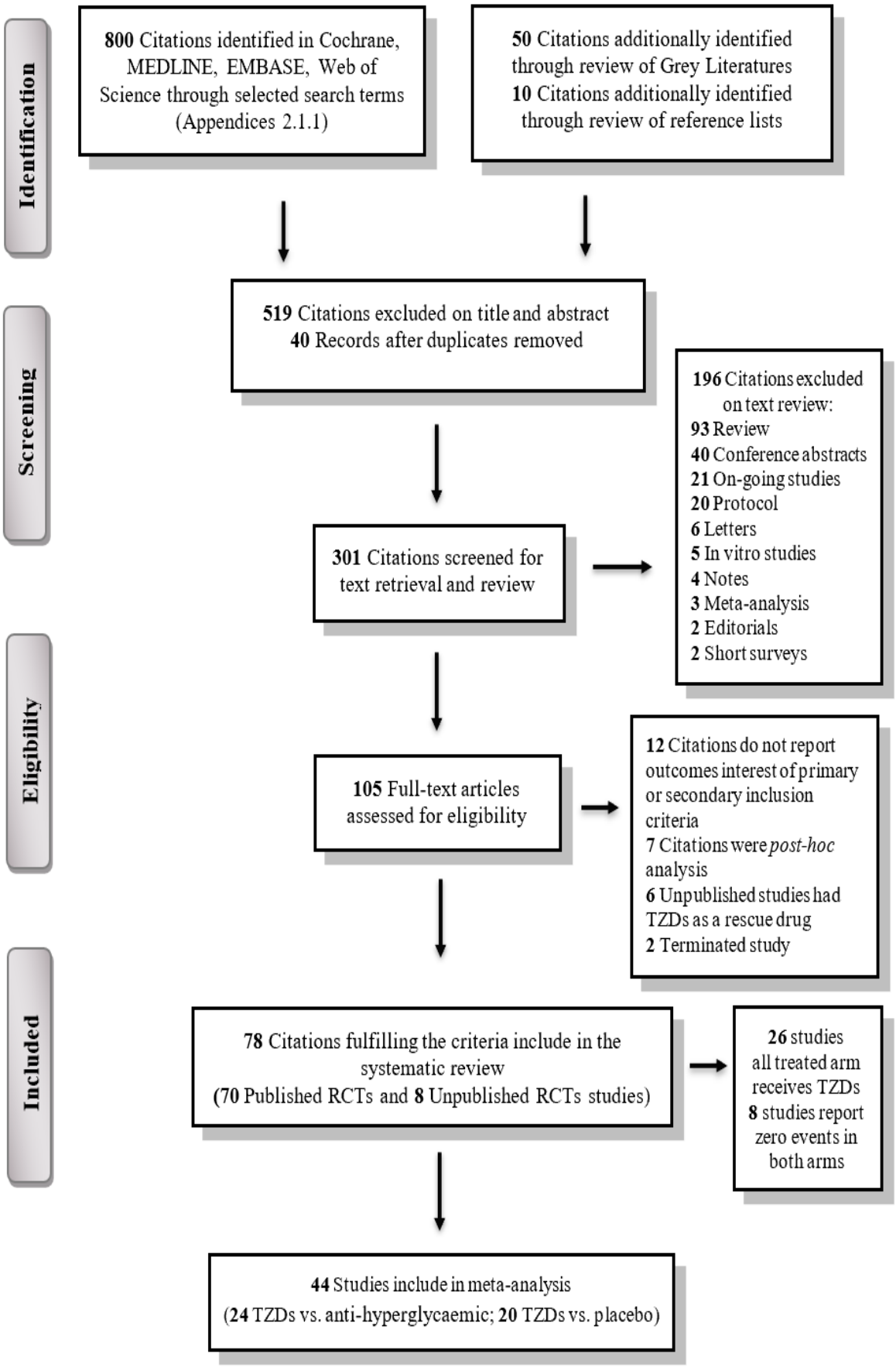

Figure 2-1. PRISMA flow chart depicting the search strategy of the studies included in the systematic review and meta-analysis.

2.3.1 Study description

With respect to study blinding, 20 trials were open-label design and 58 double-blind, randomised studies.

2.3.2 Study population

Study participants had all been diagnosed with either insulin resistance or T2DM when enrolled in these studies and were either naïve to hypoglycaemic treatment or had not achieved adequate control of blood glucose despite the use of antidiabetics drugs. From the total 78 studies, 11 trials involved nondiabetic individuals, 62 focused on people with T2DM and five focused on people with diabetes and insulin resistance. Of these, only one trial enrolled insulin resistance individuals with acute stroke. [93] The participants (10% nondiabetics, 90% diabetics) were relatively young, with average age of ≤72 years and 58% were male. Diabetes control was relatively poor, with a mean HbA_{1c} of approximately 8.5 ± 1.0%. A minority of trial participants had experienced previous strokes (2.3% to 18.8%) or TIAs (2.2% to 2.4%). From the total population, 3.8% to 15% had prior fractures and <1% with bone disease or BMD levels.

2.3.3 Study interventions and exposures

From the 78 included studies, in 21 studies their participants were naïve to drug treatment for T2DM and 57 studies their participants were exposed to various drug treatment for T2DM. In 24 studies patients were randomised to TZDs versus placebo and in 54 studies patients were randomised to TZDs versus antidiabetic therapies. Of these, in 16 trials patients were randomised to pioglitazone versus placebo and in 41 trials patients were randomised to pioglitazone versus antidiabetic therapies. The remaining 21 trials were non-pioglitazone TZDs.

Most studies employed various comparative dosing through oral or injectable administration. For pioglitazone, the dose was 15 mg administered orally per day. This dose could be titrated to 45 mg/d or to the maximally tolerated dose below this level. Additional glucose-lowering medications were used during studies according to their approved dosage in line with medical practice. The trials' follow-up length ranged from 12 to 261 weeks.

2.3.4 Risk of bias assessment

Generally, 34 studies scored as high risk for bias, eight as unclear and 36 as low risk. Typically, there was adequate descriptive data for random sequence generation. However, 20 studies were open-label design, of which six and other 20 studies had a high risk for performance bias because their participants had TZDs before their study randomisation (26 studies all participants received out treatment of interest in both arms (open-label design)). The selection and detection bias were scored as unclear in eight % of the studies (these studies were all unpublished RCTs). (Figure 2-2 and Supplemental Figure 2-1).

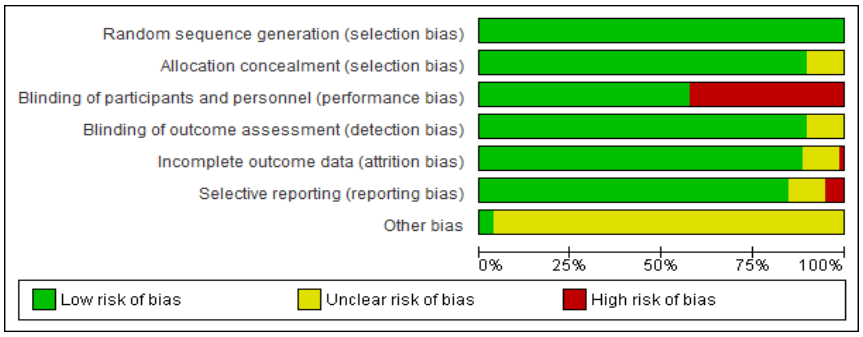

Figure 2-2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

2.4 Outcome measures

Of 78 studies, fractures occurred in 70 studies and no fractures in eight studies.

2.4.1 Studies assessing fracture subtype by severity and mechanism

From the 78 included studies, the incidence risk of fractures reported as non-serious events in 28 studies, as serious events in 38 studies, as either non-serious or serious events in 11 studies and one study reported fracture outcomes in general. All these fracture outcomes were recorded throughout the studies as part of the safety assessment process and adverse event reporting. The primary outcome for most of these trials was the change in HbA_{1c} from baseline. None of these trials were designed specifically to assess fractures as primary or secondary outcomes in insulin resistance individuals or in people with T2DM in stroke population.

2.4.2 Studies assessing fracture risk by skeletal involvement

Of 78 studies, fractures risk was stratified by skeletal location as follows: 12 studies reported by spinal location, 16 studies reported by hip location, 11 studies reported by femoral location, 11 studies reported by upper limbs location, 8 studies reported by wrist location, 12 studies reported by lower limbs location and 17 studies reported by ankles location.

2.4.3 Studies assessing fracture risk by gender

Sixteen studies reported non-serious and serious fractures by sex.

2.4.4 Studies assessing bone mineral density

Five studies examined the impacts of BMD on fractures risk.

2.5 Outcome results

The characteristics of all included trials of fractures outcome results are detailed in (Supplemental Table 2-4 and Supplemental Table 2-5). The meta-analyses are performed on 44 trials with at least one event (44 studies reported fractures with TZDs, of which 27 studies reported fractures with pioglitazone).

Of the 70 trials that studied the outcomes of fractures, no statistical difference is seen in 62 studies. In two studies, no clinically important differences are observed in patients using TZD across the groups. [340] [341] However, the fractures rates increased significantly in six trials (three studies with TZDs (rosiglitazone) [159] [125] [342] and three studies with pioglitazone [93] [94] [146]).

Generally, the outcome of fractures occurring during the follow-up period were non-serious. The consequences of these events, however, were not stated in most studies. A majority of the non-serious events were not considered by the researchers to be related to pioglitazone. However, a causal relationship could not be ruled out in a minority of the events that occurred with TZD use in five studies. [343] [344] [345] [346] [347]

2.5.1 TZDs Class

The rate of fracture was 35% where TZDs were compared to placebo and active comparators. In 44 trials, the incidence of fracture risk was significantly increased with TZDs use (RR 1.35; 95% CI 1.24−1.48; P<0.00001; I^2=10%) using fixed-effect model. There was no significant evidence of reporting bias or statistical heterogeneity across the trials (I^2=10%). The GRADE score was moderate (Supplemental Table 2-16). A summary table detailed the effects of the TZDs class on fractures risk (Table 2-1).

Outcome or Subgroup	Studies	Participants	Effect Estimate Mantel-Haenszel, Fixed-effect test Risk Ratio (95% confidence intervals)
1.1 TZDs fracture by severity and mechanism (TZDs vs. non-TZDs)	**44**	**86659**	**1.35 [1.24, 1.48]**
1.1.1 Non-serious	22	31264	1.33 [1.18, 1.48]
1.1.2 Serious	25	22959	1.30 [1.05, 1.62]
1.1.3 Low-energy	4	8564	1.51 [1.22, 1.88]
1.1.4 High-energy	6	6149	1.35 [0.89, 2.05]
1.1.5 Stress	1	3876	1.25 [0.49, 3.16]
1.1.6 Pathological	5	13847	1.47 [0.77, 2.80]

Table 2-1. A summary table detailed the effects of the TZDs class on the risk of fractures.

2.5.1.1 Fracture subtype by severity and mechanism

Both non-serious (RR 1.33; 95% CI 1.18−1.48; P<0.00001; I^2=33%) and serious fractures (RR 1.30; 95% CI 1.05−1.62; P=0.02; I^2=16%) increased with TZDs use versus no-TZDs user especially low-energy fractures from falls (RR 1.51; 95% CI 1.22−1.88; P=0.0002; I^2=0%), using fixed-effect model (Figure 2-3). However, only non-serious, low energy, but not serious, events were increased in random-effect model (Figure 2-4). The rate of high energy, stress or pathological fractures was not increased with TZDs use versus no-TZDs user in both models.

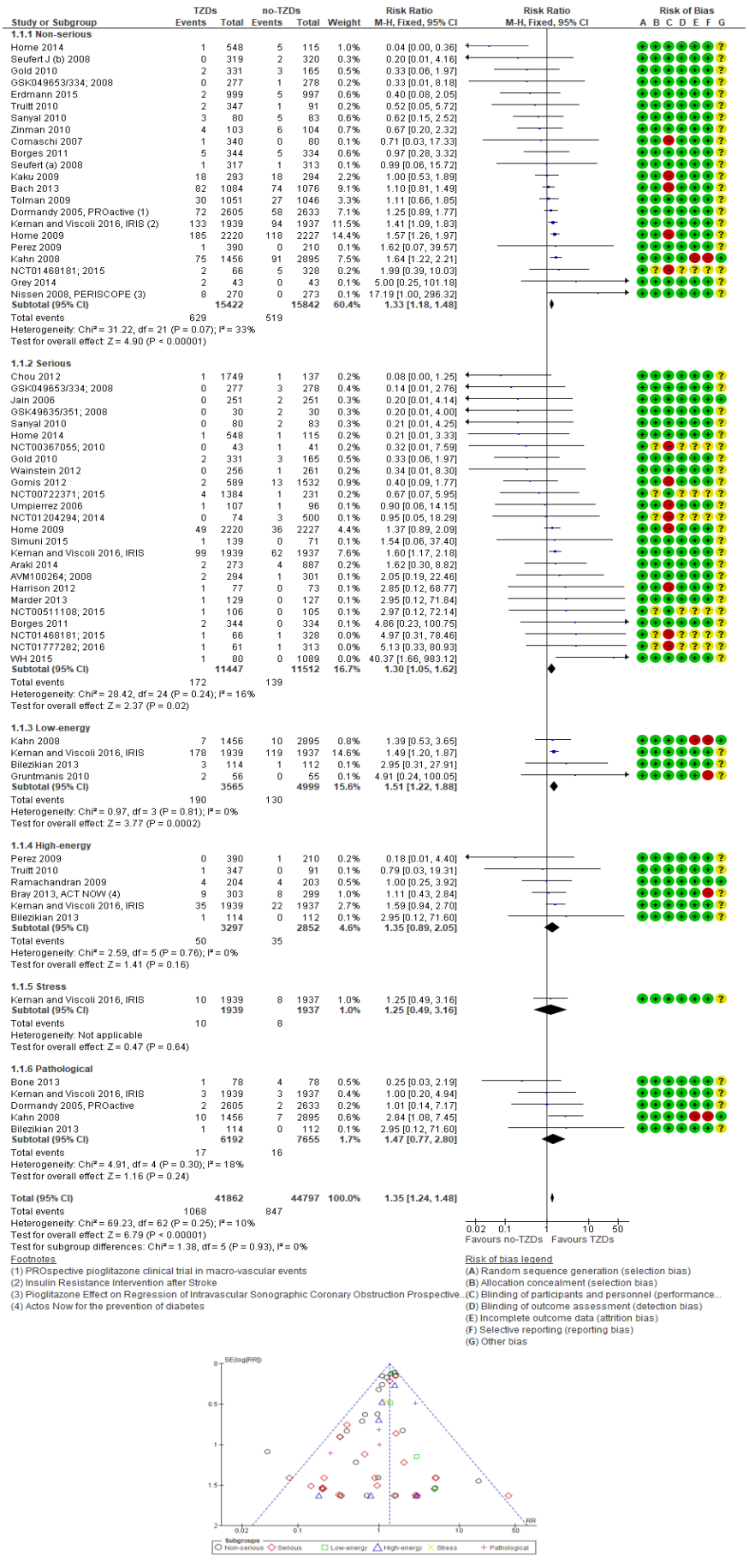

Figure 2-3. Forest and funnel plot of fracture subtype by severity and mechanism with TZDs therapies, Fixed-effect model.

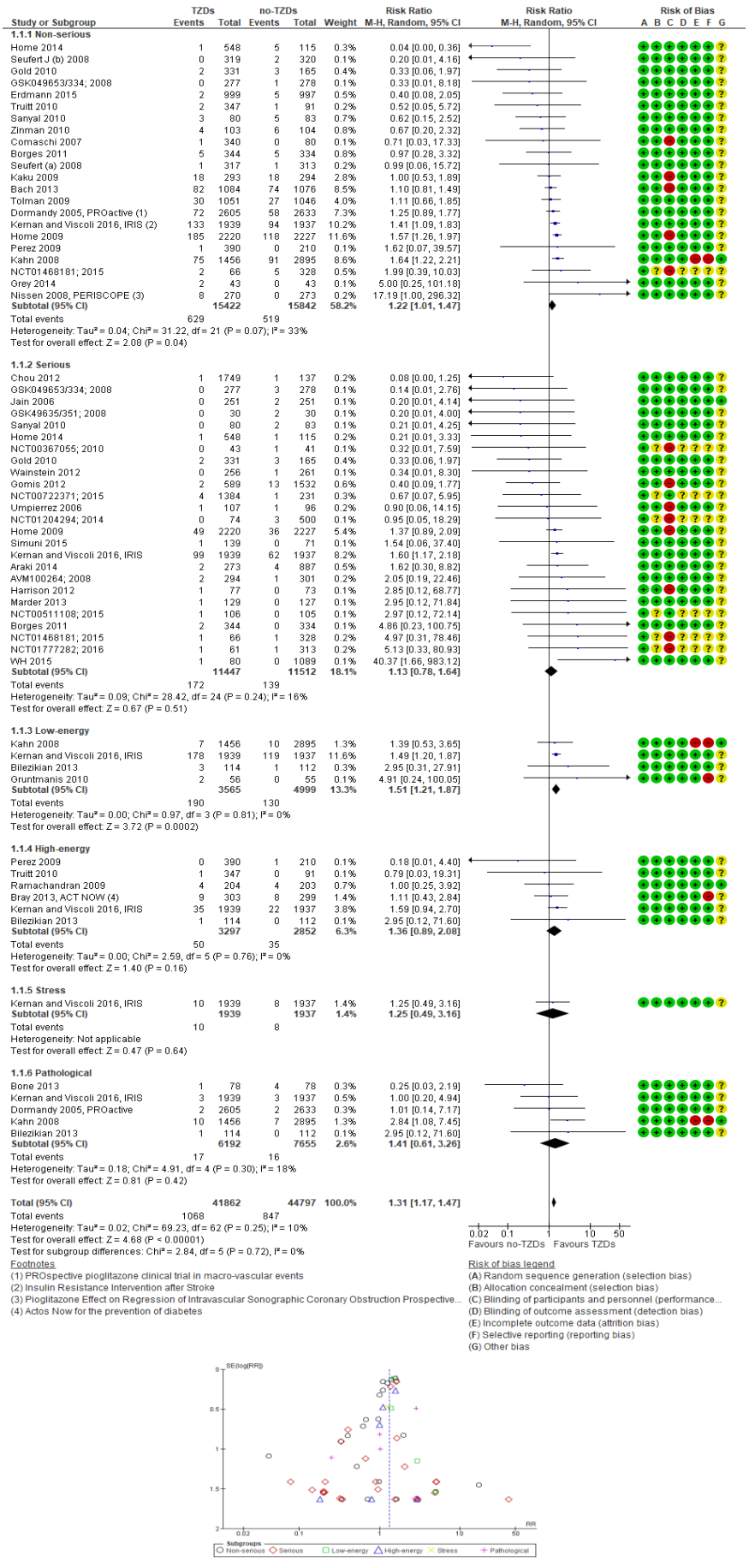

Figure 2-4. Forest and funnel plot of fracture subtype by severity and mechanism with TZDs therapies, Random-effect model.

2.5.2 Pioglitazone therapy

The rate of fracture was 19% with pioglitazone versus placebo and active comparators. In 14 trials comparing pioglitazone versus placebo (13,451 participants; 449 fractures), pioglitazone increased the incidence rate of fracture (RR 1.21; 95% CI 1.01−1.45; P=0.04; I^2=32%) using fixed-effect model (Figure 2-5). In 13 trials, comparing pioglitazone with active comparators (11,267 participants; 99 fractures) there was no increased in the incidence rate of fracture (RR 1.08; 95% CI 0.73−1.59; P=0.70; I^2=15%) using fixed-effect model (Figure 2-5). No difference in the incidence of fractures was noted in the pooled data from random-effect model (Figure 2-6). There was no significant evidence of reporting bias or statistical heterogeneity across the trials (I^2=23%). The GRADE score was moderate (Supplemental Table 2-17 and Supplemental Table 2-18). A summary table detailed the effects of the pioglitazone on fractures risk (Table 2-2).

Outcome or Subgroup	Studies	Participants	Effect Estimate Mantel-Haenszel, Fixed-effect test Risk Ratio (95% confidence intervals)
2.1 Pioglitazone fracture by treatment allocation	**27**	**24718**	**1.19 [1.01, 1.40]**
2.1.1 Pioglitazone vs. placebo	14	13451	1.21 [1.01, 1.45]
2.1.2 Pioglitazone vs. control	13	11267	1.08 [0.73, 1.59]
3.1 Pioglitazone fracture by severity, mechanism and treatment allocation (placebo)	**14**	**39076**	**1.36 [1.20, 1.53]**
3.1.1 Non-serious	7	10794	1.25 [1.03, 1.51]
3.1.2 Serious	7	6194	1.48 [1.10, 1.98]
3.1.3 Low-energy	1	3876	1.49 [1.20, 1.87]
3.1.4 High-energy	4	5066	1.43 [0.93, 2.20]
3.1.5 Stress	1	3876	1.25 [0.49, 3.16]
3.1.6 Pathological	3	9270	0.67 [0.24, 1.87]
3.2 Pioglitazone fracture by severity, mechanism and treatment allocation (controls)	**13**	**11867**	**1.07 [0.73, 1.56]**
3.2.1 Non-serious	6	4929	1.28 [0.81, 2.01]
3.2.2 Serious	7	6338	0.71 [0.32, 1.55]
3.2.3 High-energy	1	600	0.18 [0.01, 4.40]
4.1 Pioglitazone fracture by skeletal location and treatment allocation	**16**	**59308**	**1.58 [1.32, 1.91]**
4.1.1 Spine pioglitazone vs. placebo	3	9777	2.13 [1.28, 3.55]
4.1.2 Spine pioglitazone vs. control	1	2121	0.87 [0.04, 21.23]
4.1.3 Hip pioglitazone vs. placebo	3	9370	1.38 [0.84, 2.28]
4.1.4 Hip pioglitazone vs. control	2	2241	1.10 [0.12, 9.99]
4.1.5 Femur pioglitazone vs. placebo	1	3876	8.99 [0.48, 166.88]
4.1.6 Femur pioglitazone vs. control	2	2638	0.53 [0.06, 4.79]
4.1.7 Upper limbs pioglitazone vs. placebo	2	9114	1.37 [0.98, 1.93]
4.1.8 Upper limbs pioglitazone vs. control	2	2158	1.43 [0.18, 11.54]
4.1.9 Distal upper limbs (wrist) pioglitazone vs. placebo	1	602	6.91 [0.36, 133.16]
4.1.10 Distal upper limbs (wrist) pioglitazone vs. control	2	1143	1.23 [0.18, 8.38]
4.1.11 Lower limbs pioglitazone vs. placebo	3	9264	1.85 [1.33, 2.56]
4.1.12 Lower limbs pioglitazone vs. control	2	2664	2.43 [0.32, 18.41]
4.1.13 Distal lower limbs (ankle) pioglitazone vs. placebo	5	1717	0.63 [0.21, 1.90]
4.1.14 Distal lower limbs (ankle) pioglitazone vs. control	2	2623	0.37 [0.05, 2.94]
5.1 Pioglitazone fracture in females	**8**	**5315**	**1.56 [1.20, 2.02]**
5.1.1 Females versus placebo	3	3269	1.56 [1.17, 2.07]
5.1.2 Females versus control	5	2046	1.55 [0.84, 2.86]
5.2 Pioglitazone fracture in males	**6**	**8149**	**1.10 [0.84, 1.43]**
5.2.1 Males versus placebo	2	6001	1.13 [0.84, 1.52]
5.2.2 Males versus control	4	2148	0.95 [0.49, 1.82]
6.1 Pioglitazone BMD by skeletal location (placebo)	**3**	**851**	**-0.23 [-0.36, -0.09]**
6.1.1 Lumbar spine	3	646	-0.18 [-0.34, -0.03]
6.1.2 Hip	1	86	-0.53 [-0.96, -0.10]
6.1.3 Femural neck	1	119	-0.25 [-0.61, 0.11]

Table 2-2. A summary table detailed the effects of pioglitazone therapy on the risk of fractures.

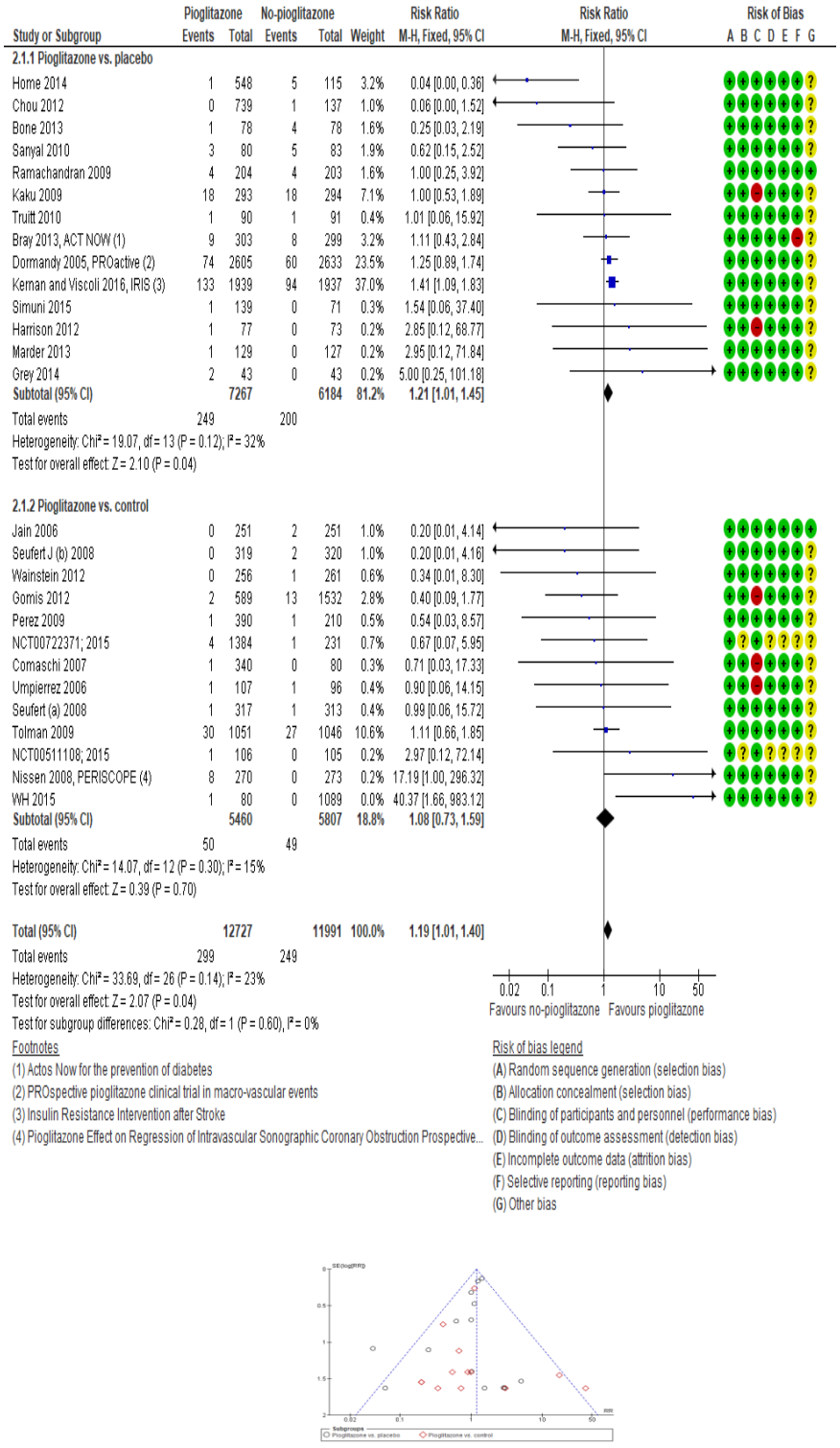

Figure 2-5. Forest and funnel plot of fracture by treatment allocation with pioglitazone therapy, Fixed-effect model.

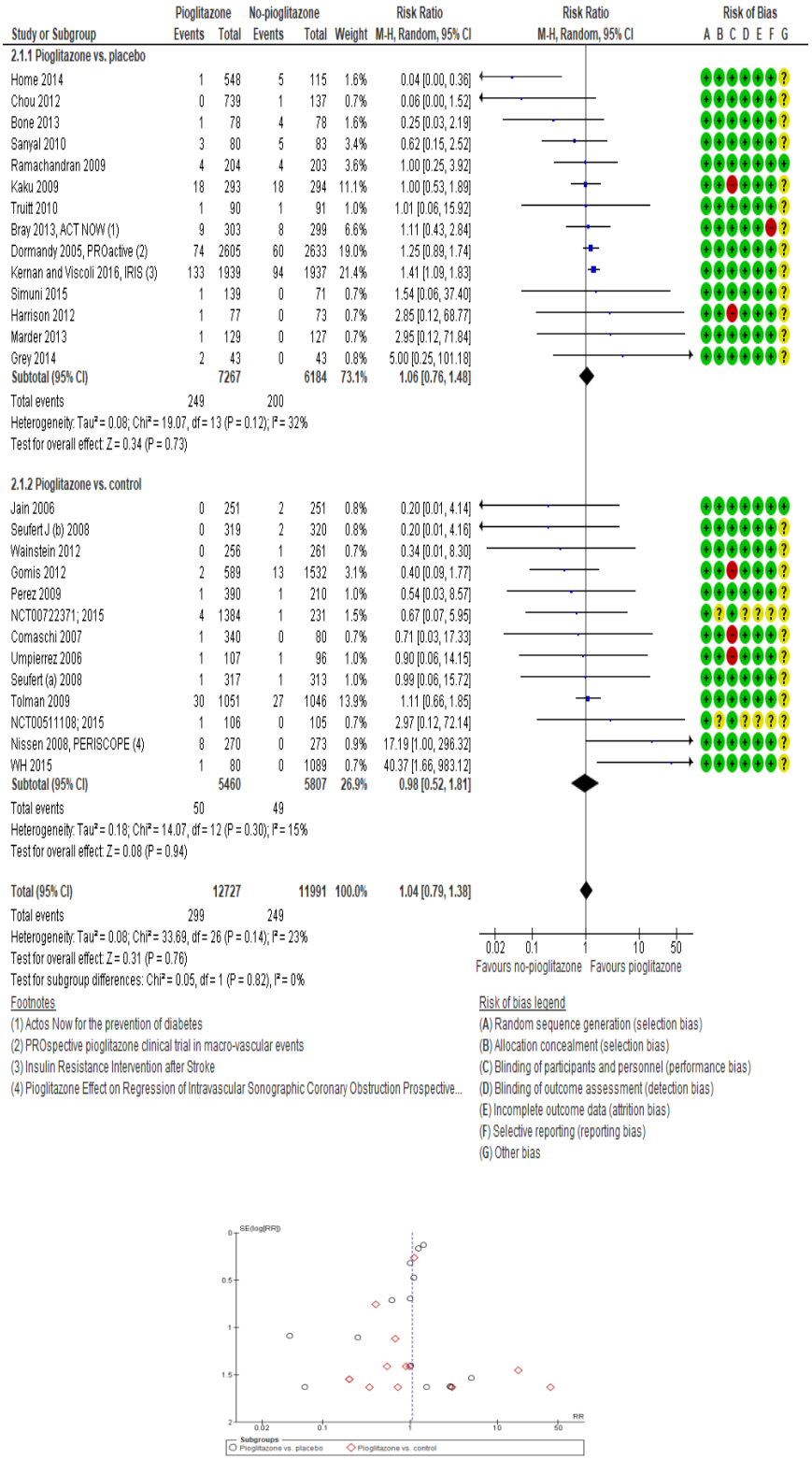

Figure 2-6. Forest and funnel plot of fracture by treatment allocation with pioglitazone therapy, Random-effect model.

2.5.2.1 Fracture subtype by severity and mechanism

In 14 trials comparing pioglitazone versus placebo, both non-serious (RR 1.25; 95% CI 1.03−1.51; *P*=0.02; I^2=53%) and serious events (RR 1.48; 95% CI 1.10−1.98; *P*=0.01; I^2=24%) increased with pioglitazone, especially low-energy fractures from falls (RR 1.49; 95% CI 1.20−1.87; *P*=0.0004), using fixed-effect model (Figure 2-7) but not with random-effect model (Figure 2-8). The rate of high energy, stress or pathological fractures was not increased with pioglitazone use versus no-pioglitazone user in both models.

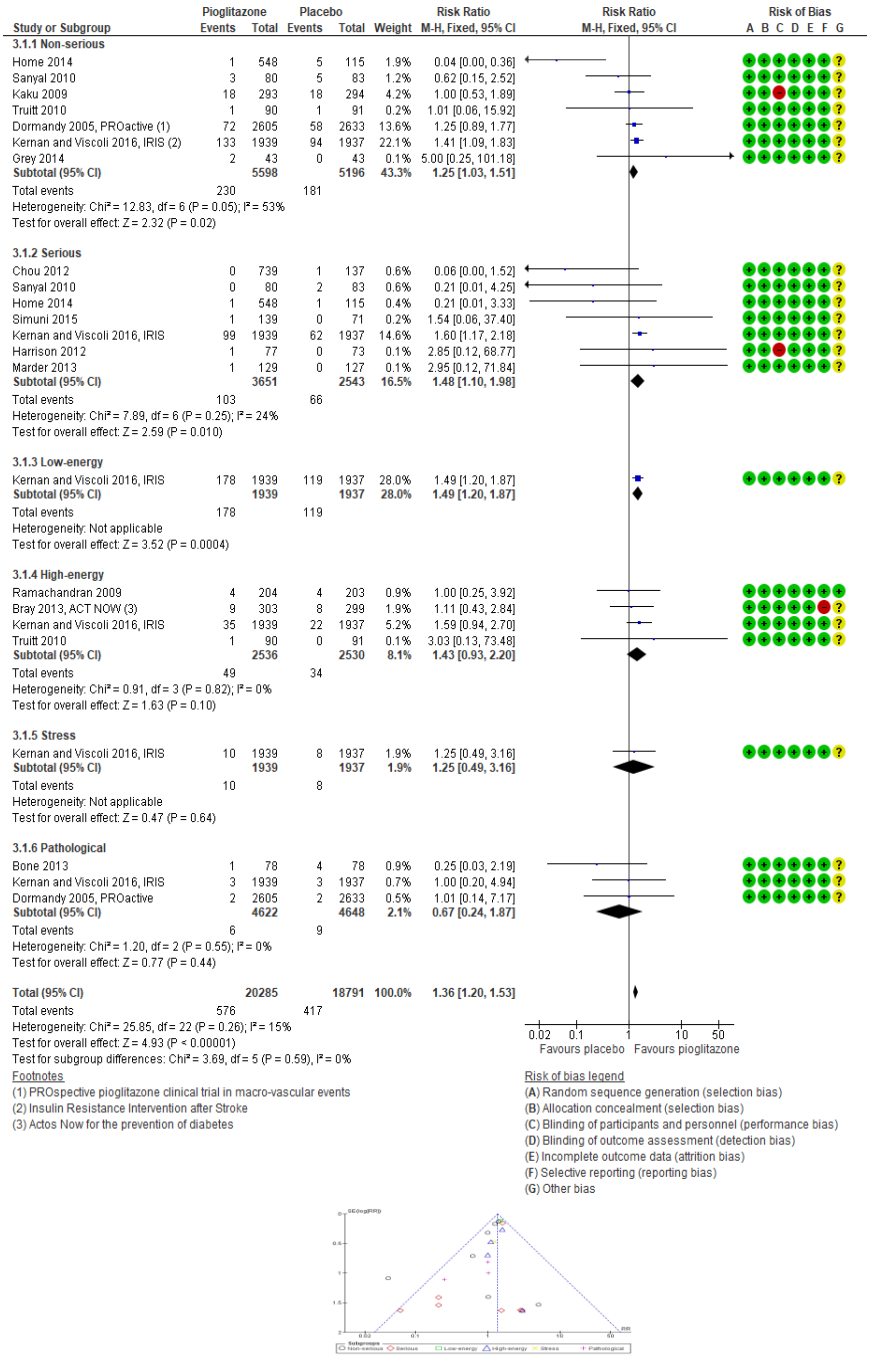

Figure 2-7. Forest and funnel plot of fracture subtype by severity and mechanism with pioglitazone versus placebo, Fixed-effect model.

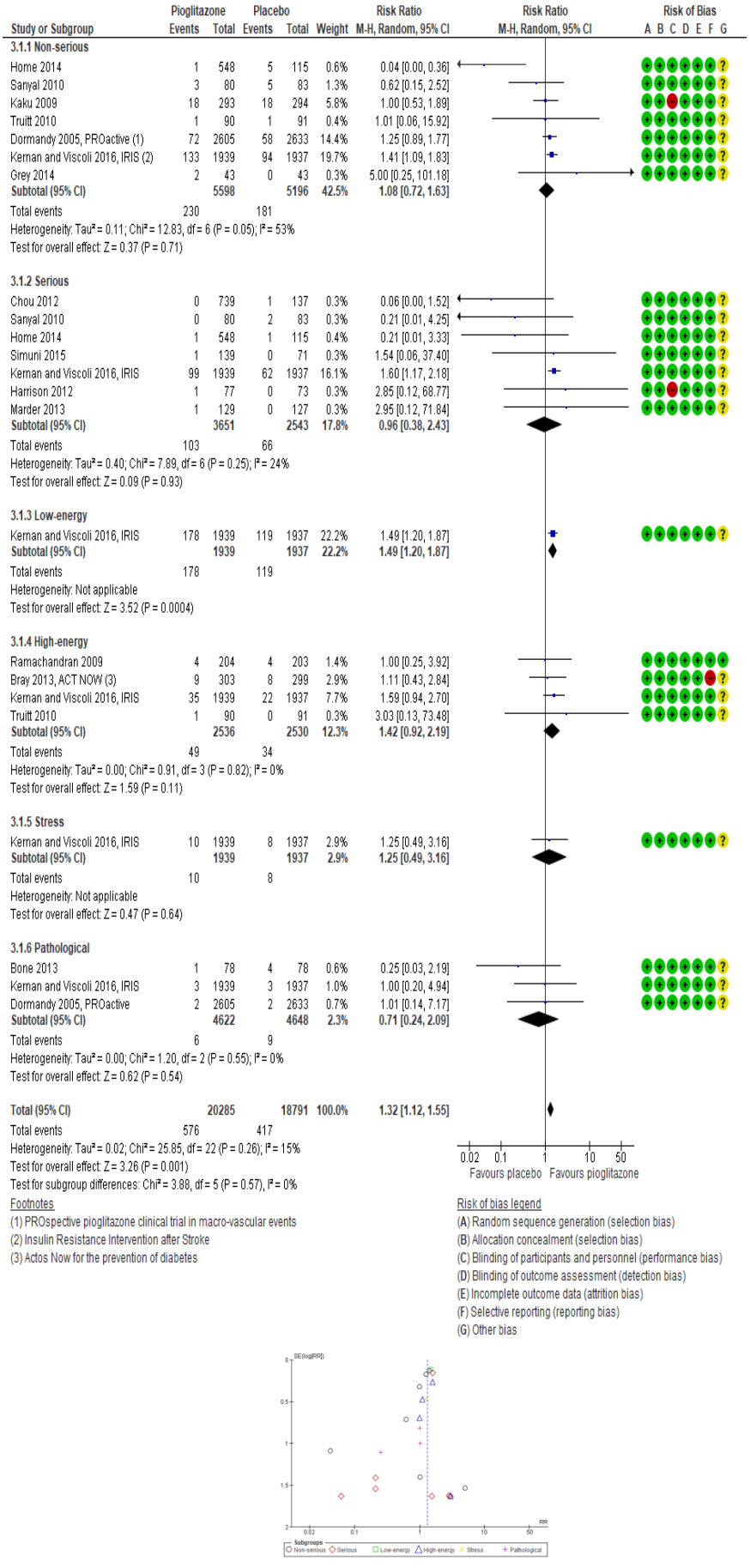

Figure 2-8. Forest and funnel plot of fracture subtype by severity and mechanism with pioglitazone versus placebo, Random-effect model.

In 13 trials comparing pioglitazone with active comparators, both non-serious (RR 1.28; 95% CI 0.81−2.01; *P*=0.29; I^2=2%) and serious events (RR 0.71; 95% CI 0.32−1.55; *P*=0.38; I^2=29%) were did not increase with pioglitazone using fixed-effect (Figure 2-9) and random-effect model (Figure 2-10).

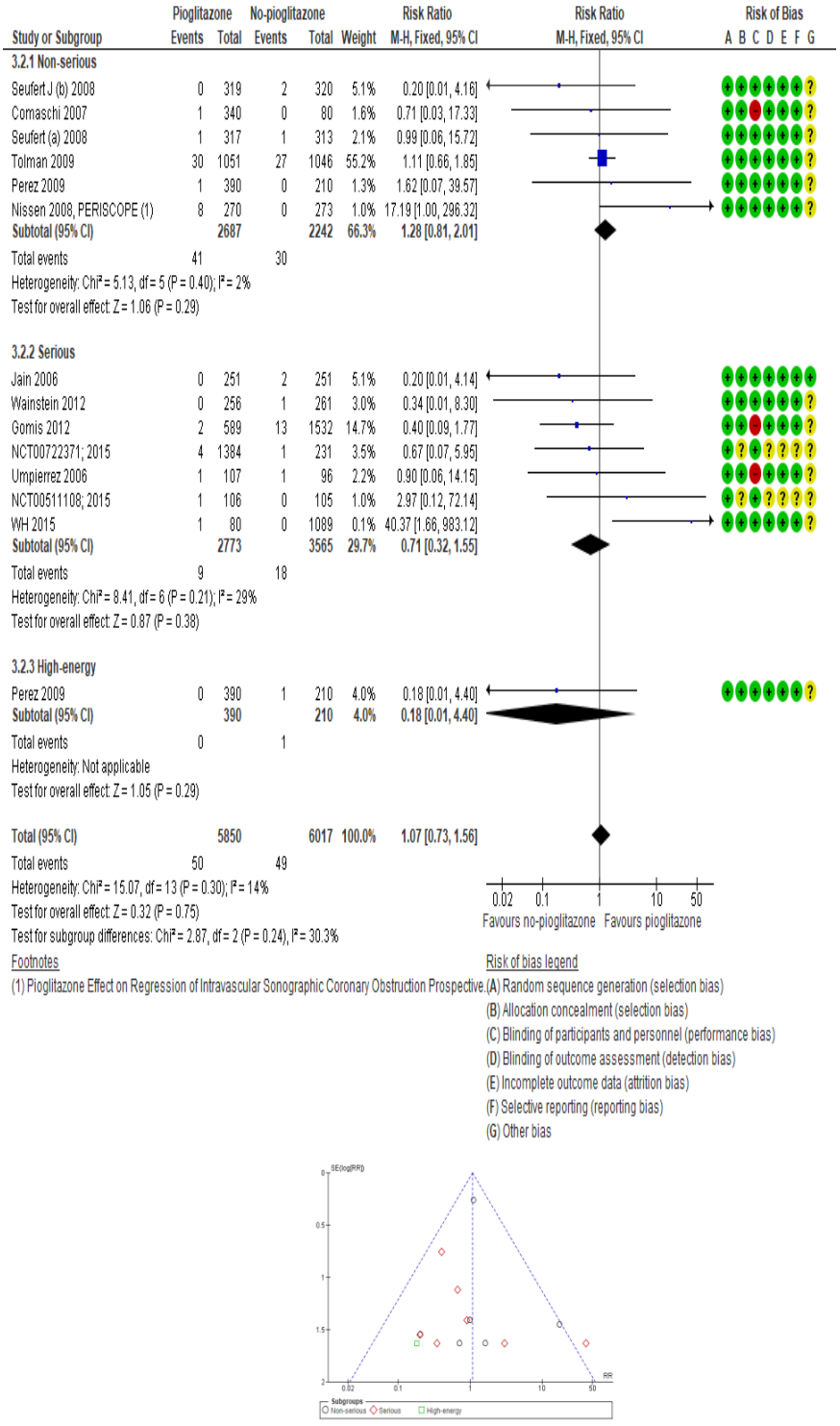

Figure 2-9. Forest and funnel plot of fracture subtype by severity and mechanism with pioglitazone versus active comparators, Fixed-effect model.

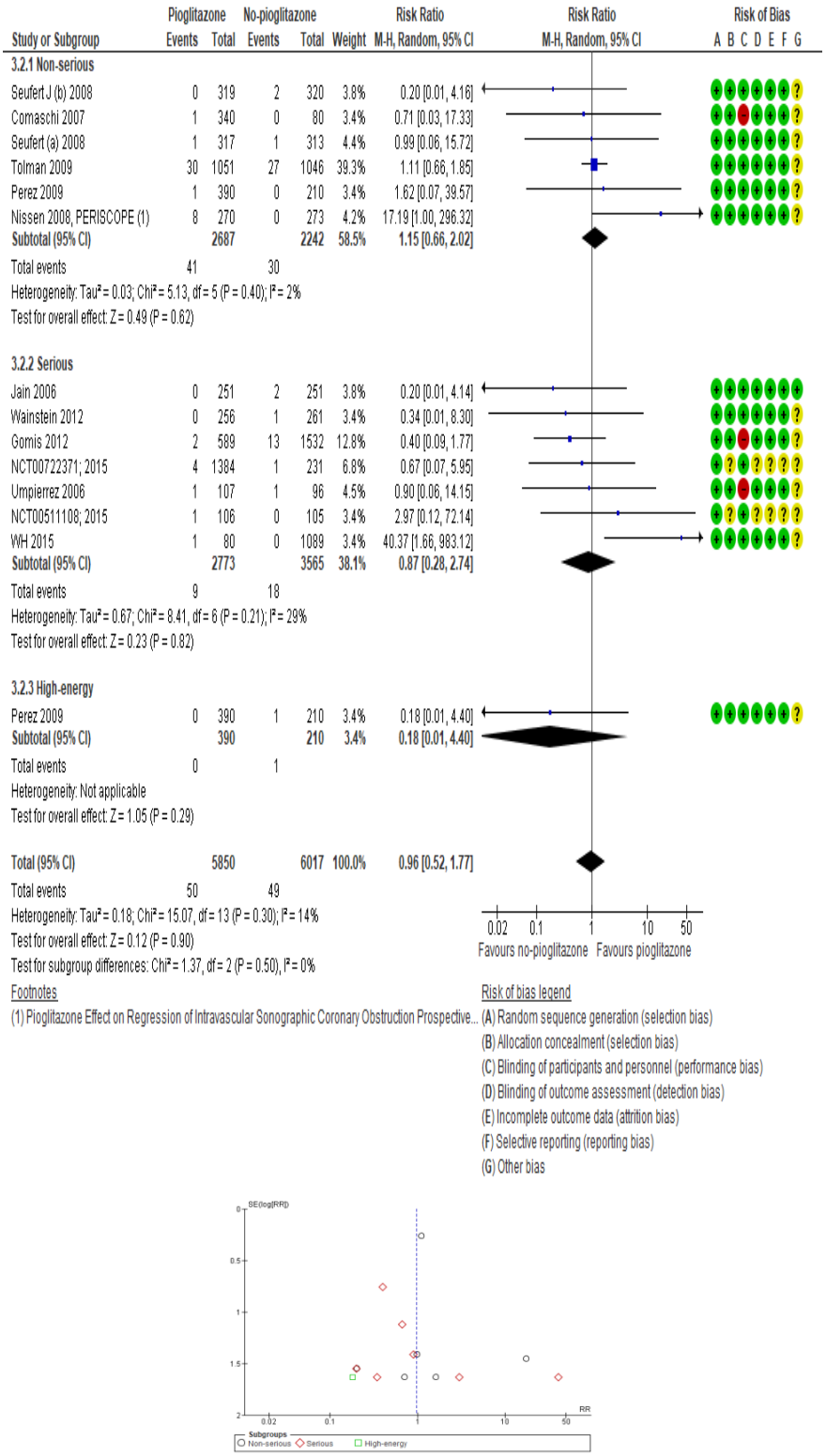

Figure 2-10. Forest and funnel plot of fracture subtype by severity and mechanism with pioglitazone versus active comparators, Random-effect model.

2.5.2.2 Fracture outcomes by skeletal involvement

The characteristics of trials that reported fractures by anatomical site are detailed in Supplemental Table 2-6 (spine), Supplemental Table 2-7 (hip), Supplemental Table 2-8 (femur), Supplemental Table 2-9 (upper limbs), Supplemental Table 2-10 (wrist), Supplemental Table 2-11 (lower limbs) and (Supplemental Table 2-12 (ankles).

A majority of the fracture outcomes studied according to bone involvement appeared to be non-serious events. Of the 29 trials that studied fracture outcomes by anatomical site, no difference in fracture rates was seen across the groups in 26 trials but fractures rates significantly increased in three trials: one study with the TZD rosiglitazone, [125] involving the spine, upper limbs and lower limbs, and two studies with the TZD pioglitazone, involving the upper limbs and lower limbs [94] and the spine, upper limbs and lower limbs. [141]

Compared to placebo, but not to active comparators, the number of fractures in patients treated with pioglitazone increased in the spine (9,777 participants; 63 fractures) (RR 2.13; 95% CI 1.28−3.55; P=0.004; I^2=66%) and lower-extremities (9,164 participants, 154 fractures) (RR 1.85; 95% CI 1.33−2.56; P=0.0002; I^2=0%) using fixed-effect model (Figure 2-11). However, compared to placebo, but not to active comparators, fractures did not increase in the hip (9,370 participants; 60 fractures) (RR 1.38; 95% CI 0.84−2.28; P=0.20; I^2=0%), the femur (3,896 participants; 4 fractures) (RR 8.99; 95% CI 0.48−166.88; P=0.14), the upper-extremities (9,114 participants; 133 fractures) (RR 1.37; 95% CI 0.98−1.93; P=0.07; I^2=61%), the wrist (602 participants; 3 fractures) (RR 6.91; 95% CI 0.36−133.16; P=0.20) or in the ankle (1,717 participants; 9 fractures) (RR 0.63; 95% CI 0.21−1.90; P=0.41; I^2=0%) using fixed-effect model (Figure 2-11). However, lower-limbs fractures in patients taking pioglitazone versus placebo were increased in random-effect model (Figure 2-12). There was no significant evidence of reporting bias or statistical heterogeneity across the trials (I^2=0%). The GRADE score was moderate (Supplemental Table 2-19).

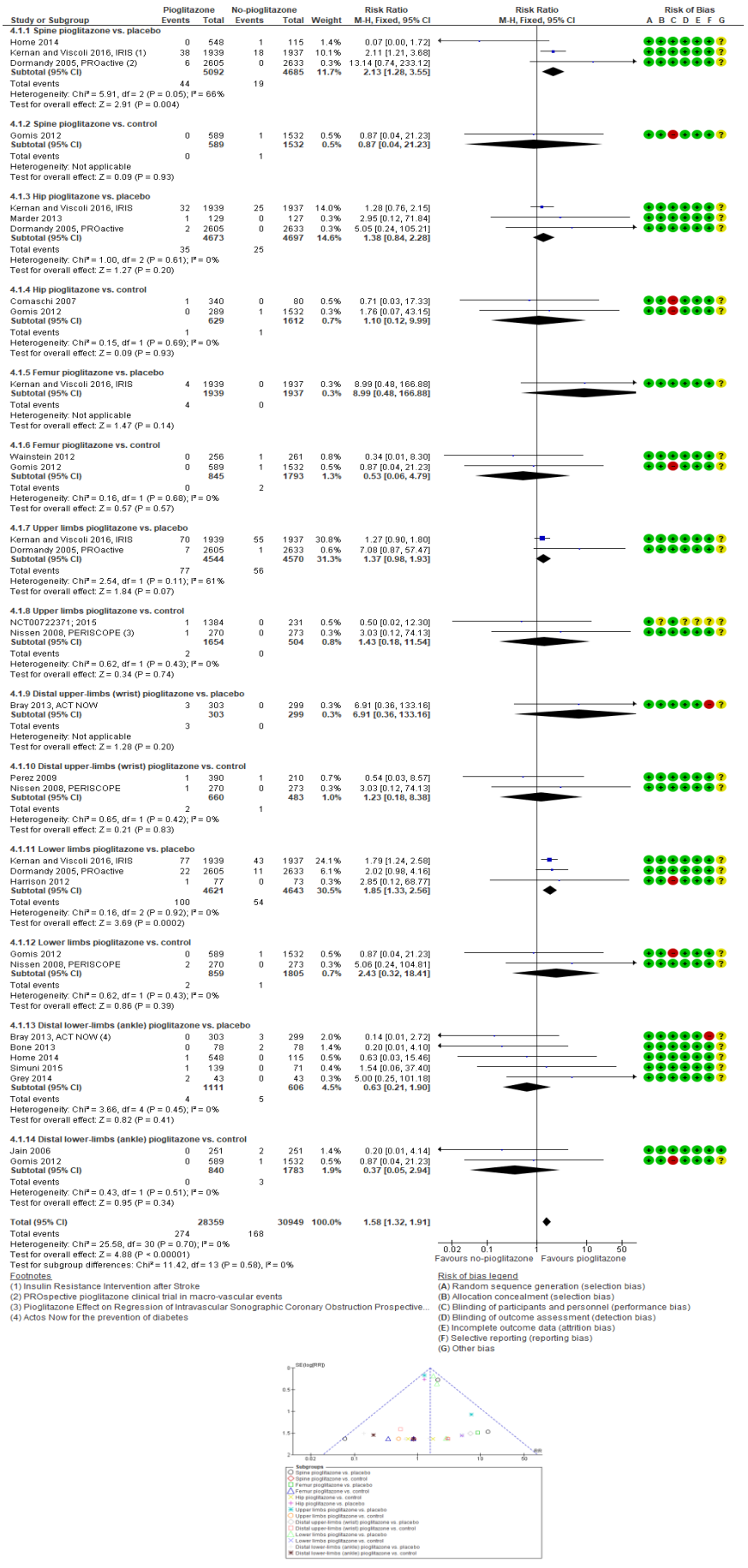

Figure 2-11. Forest and funnel plot of fracture by skeletal involvement with pioglitazone versus placebo and active comparators, Fixed-effect model.

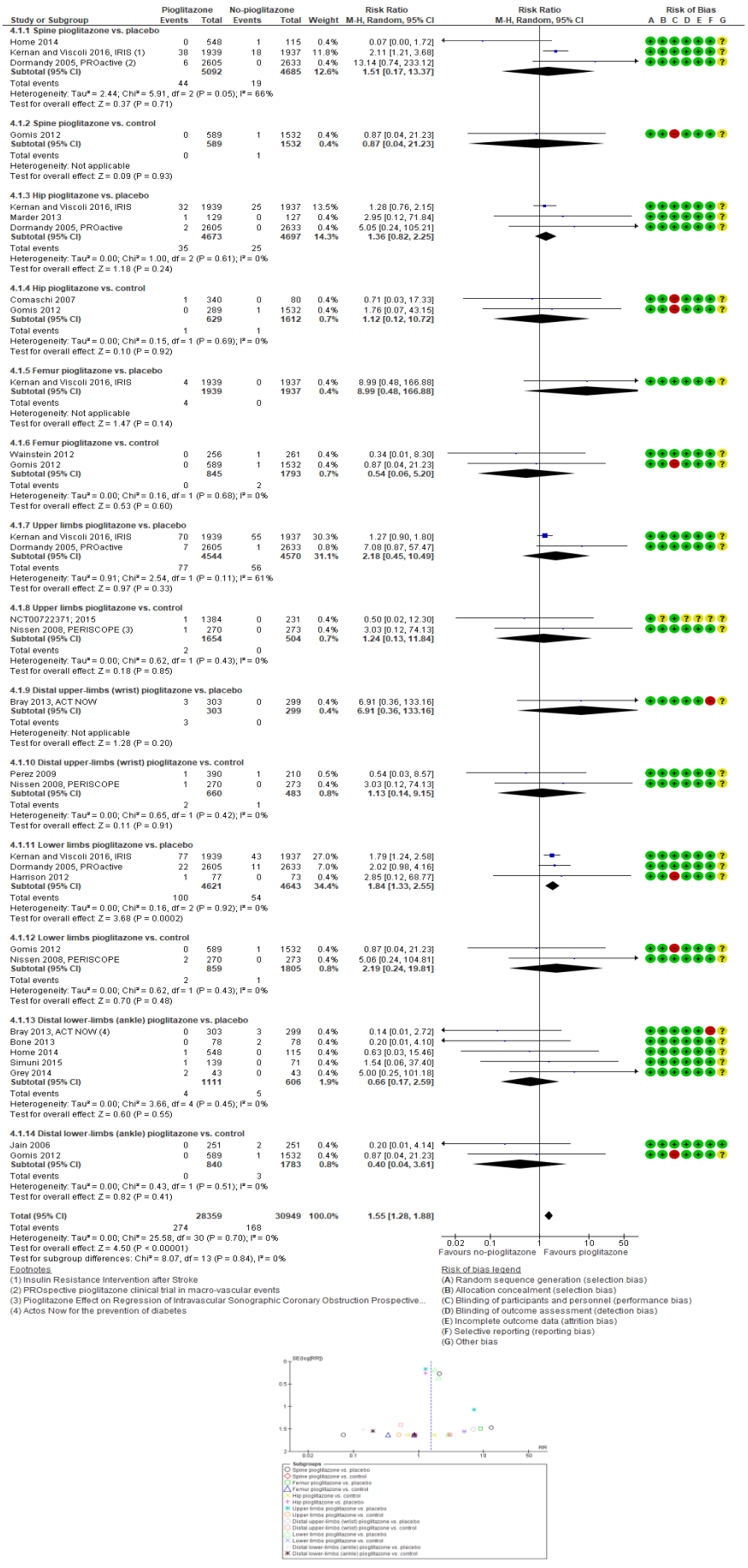

Figure 2-12. Forest and funnel plot of fracture by skeletal involvement with pioglitazone versus placebo and active comparators, Random-effect model.

2.5.2.3 Fracture outcomes by gender

The characteristics of all included trials of non-serious and serious fractures outcome results by gender were detailed in (Supplemental Table 2-13 and Supplemental Table 2-14).

Of the 16 trials that studied fracture outcomes by gender, the fracture rates were low and comparable between females and males in 10 of the trials. In six studies, however, the fracture rate increased with TZDs versus placebo; two studies considered the use of the TZD rosiglitazone in women [125] and in men and women, [159] and three studies used the TZD pioglitazone in post-menopausal women, [140] in both genders, [141] [146] and in men (the latter two studies the fracture rates increased with placebo versus pioglitazone). [140] [342]

When pioglitazone was compared to placebo, the incidence rate of fractures increased in females (RR 1.56; 95% CI 1.20−2.02; P=0.0008; I^2=0%) using fixed-effect (Figure 2-13) and random-effect model (Figure 2-14) but not with active comparators. However, the incidence rate of fractures did not increase in males (RR 1.10; 95% CI 0.84−1.43; P=0.49; I^2=14%) in studies of pioglitazone versus placebo and active comparators using fixed-effect (Figure 2-15) and random-effect model (Figure 2-16). There was no significant evidence of reporting bias or statistical heterogeneity across the trials (I^2=0%). The GRADE score was high (Supplemental Table 2-20).

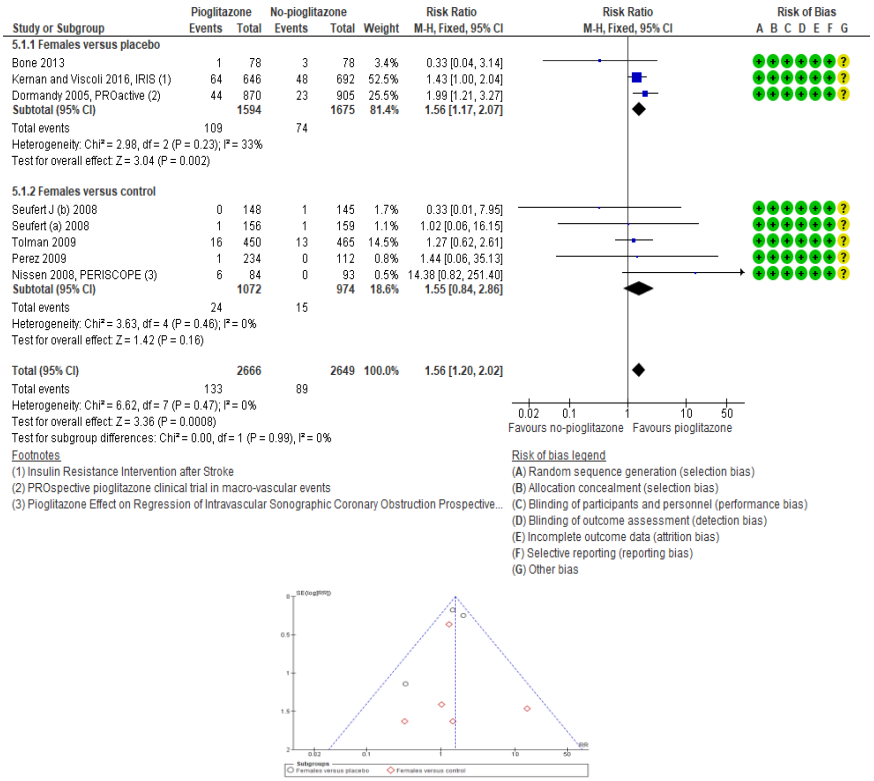

Figure 2-13. Forest and funnel plot of fracture in females with pioglitazone versus placebo and active comparators, Fixed-effect model.

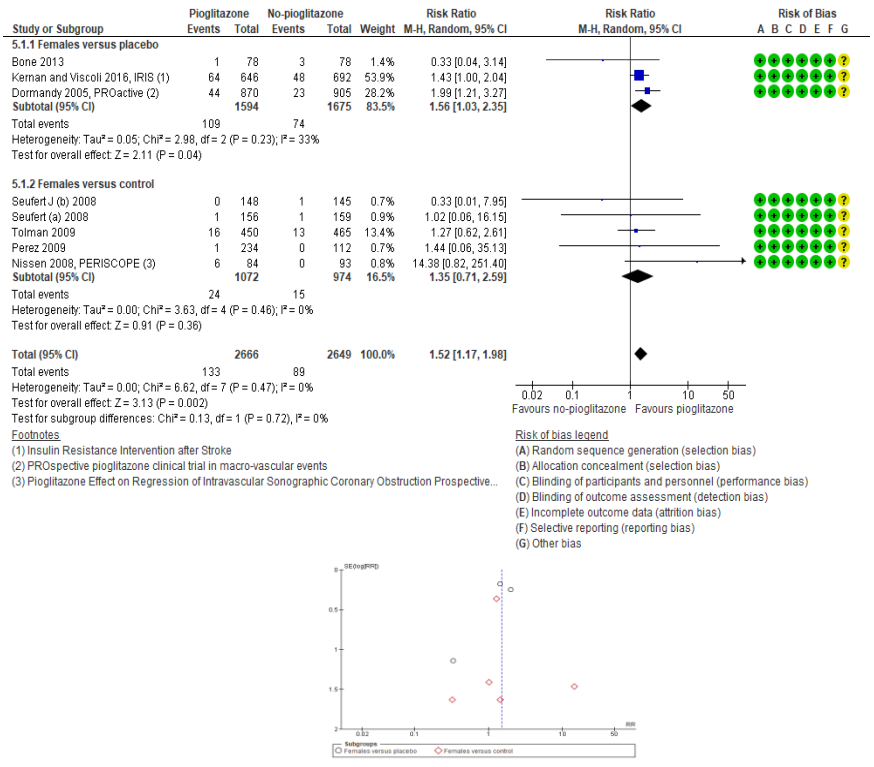

Figure 2-14. Forest and funnel plot of fracture in females with pioglitazone versus placebo and active comparators, Random-effect model.

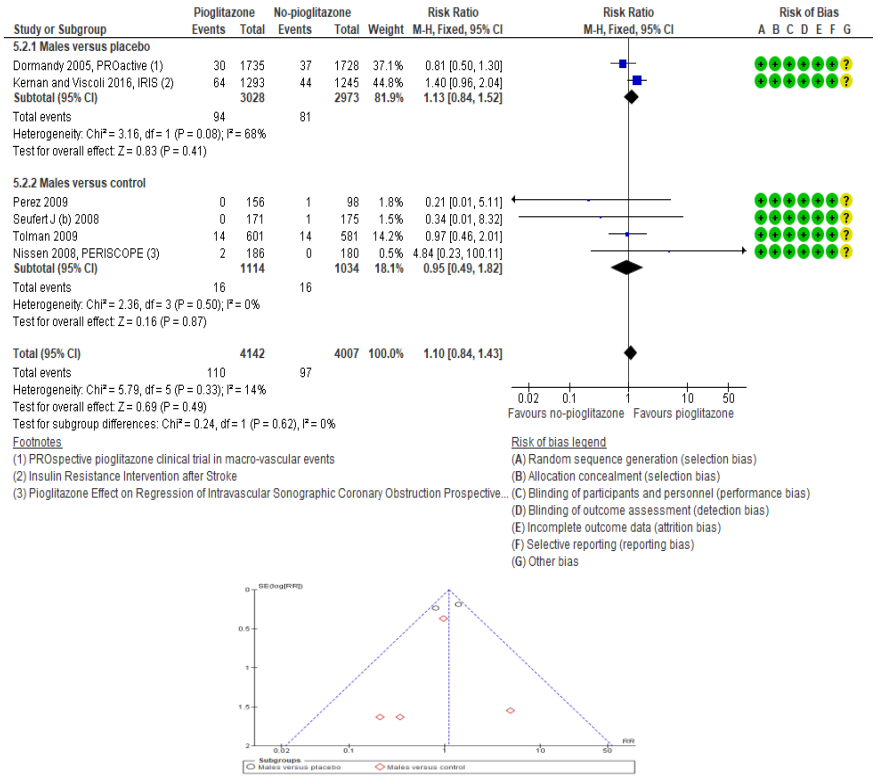

Figure 2-15. Forest and funnel plot of fracture in males with pioglitazone versus placebo and active comparators, Fixed-effect model.

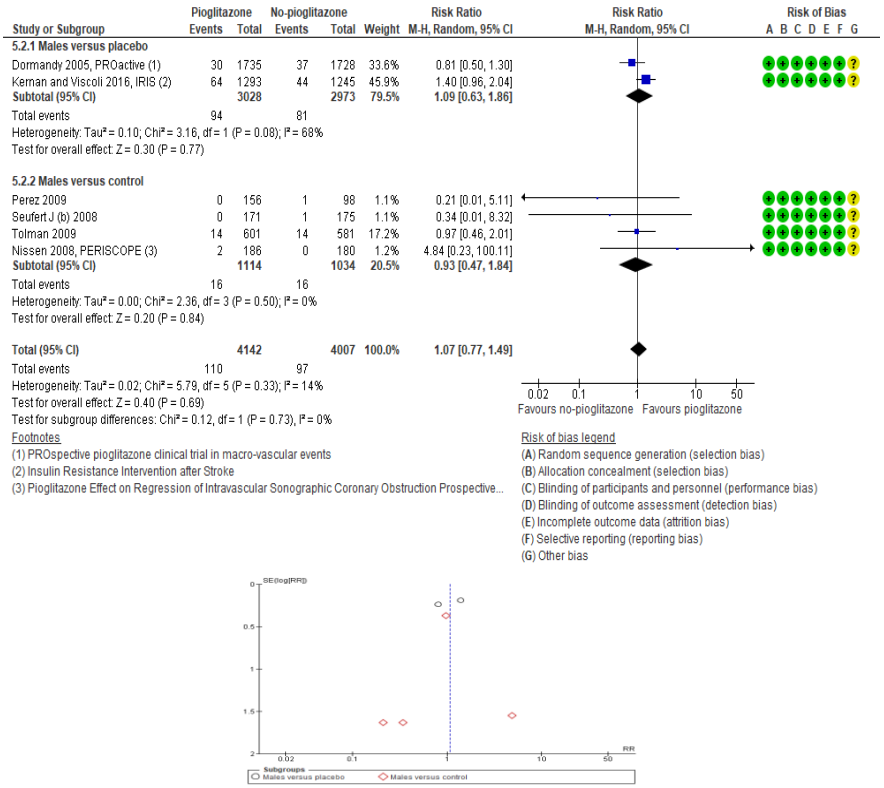

Figure 2-16. Forest and funnel plot of fracture in males with pioglitazone versus placebo and active comparators, Random-effect model.

2.5.2.4 Bone mineral density

The characteristics of all included trials of fractures outcome results and BMD levels were detailed in (Supplemental Table 2-15).

The data on BMD and the risk of fractures were minimal. Of the five studies that considered fracture outcomes and BMD levels, the fracture rates were low and comparable across groups. In two studies that looked at the use of the TZD rosiglitazone in postmenopausal women, the BMD of the hip and FN [348] after 12 months of treatment and the BMD of the LS and hip [349] after 18 months of treatment decreased significantly. However, no significant impact was seen on BMD or bone remodelling markers in the LS, FN or proximal femur in postmenopausal women after 12 to 18 months of pioglitazone use; in this study, one pioglitazone-treated and three placebo-treated women experienced confirmed fractures after treatment. [350] In another study, significant bone loss was evident in the proximal femur (hip) without any significant changes in the LS, in the BMD levels or in the biochemical markers of the bone after 12 months of pioglitazone use. [351] However, the mean BMD was reduced in both genders in the pelvis and in more males in the LS in patients using pioglitazone; no fractures were observed in these areas. [352]

In studies comparing pioglitazone with placebo, standardised mean difference (SMD) levels were decreased with pioglitazone and by the greatest amount in the LS (646 participants) (SMD -0.18; 95% CI -0.34 to -0.03; P=0.02; I^2=0%) and hip (86 participants) (SMD -0.53; 95% CI -0.96 to -0.10; P=0.02) but not in the FN (119 participants) (SMD -0.25; 95% CI -0.61 to 0.11; P=0.17) using fixed-effect (Figure 2-17) and random-effect model (Figure 2-18). There was no significant evidence of reporting bias or statistical heterogeneity across the trials (I^2=0%). The GRADER score was low (Supplemental Table 2-21).

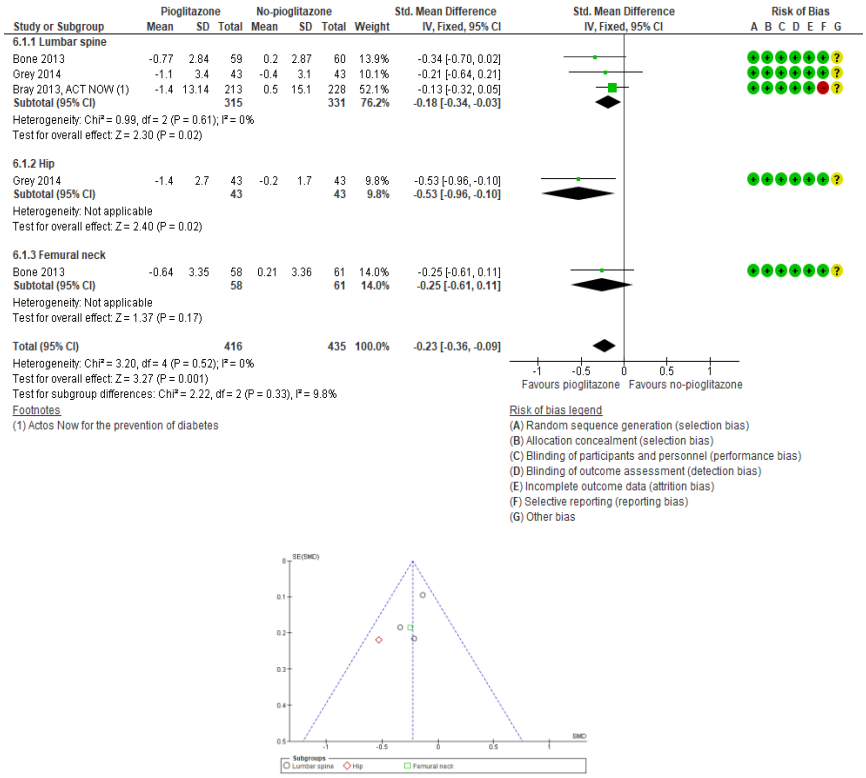

Figure 2-17. Forest and funnel plot of fracture and bone mineral density with pioglitazone versus placebo and active comparators, Fixed-effect model.

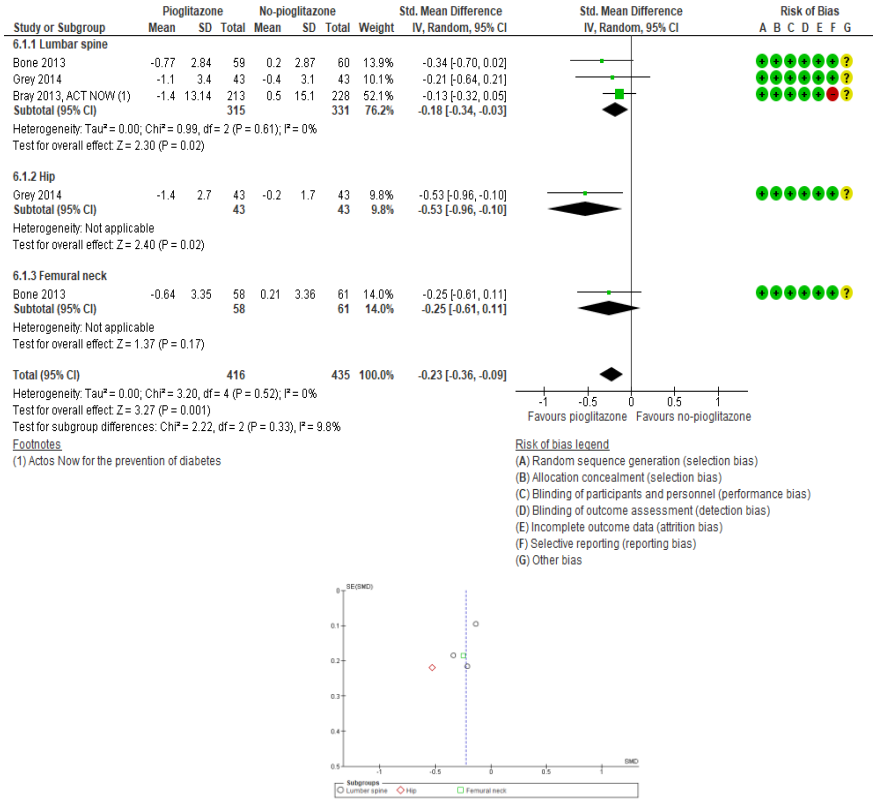

Figure 2-18. Forest and funnel plot of fracture and bone mineral density with pioglitazone versus placebo and active comparators, Random-effect model.

2.6 Discussion

The increased fracture risk that accompanies TZD use is an important clinical issue. We conducted a detailed review and meta-analysis to better understand the risk of fracture that comes with TZDs and to inform the risk/benefit ratio for clinical use or in future studies. For TZDs, we found a 2.6% increase in AR for fractures across both the nondiabetic and diabetic populations. Non-serious and serious fractures increased after 24 months of TZD exposure.

We focussed our analyses on pioglitazone, as many TZD classes have been withdrawn from the market due to their serious adverse effects profile. [353] We found that the risk of any fractures increased with pioglitazone use versus placebo (AR 3.4%; ARD 0.2%). We also found that non-serious (AR 4.1%; ARD 0.6%) and serious fractures (AR 2.8%; ARD 0.2%) increased, especially low energy fractures from falls (AR 9.2%; ARD 3.1%), in patients treated with pioglitazone for longer than 24 months versus those treated with placebo (Supplemental Figure 2-2 and Supplemental Figure 2-3). It is debatable from a rigorous statistical perspective whether such inference arose from un-monitored events or was caused by hidden confounding factors such as prior fracture risk factors as falls, diabetes severity, sex or the impacts of other anti-hyperglycaemic agents.

Diabetes is a significant independent risk factor for stroke. It increases the macro- and microvascular diabetes-related complications such as strokes, [215] orthostatic hypotension, peripheral neuropathy or limb deformity. [354] Also, hyperglycaemia is toxic to bone cells; [355] it decreases their turnover, [356] alters collagen glycosylation [357] and osteodystrophy, [358] and can increase the risk of falls and fracture. [359] We found that increased fracture risk from pioglitazone use is more evident in nondiabetic post-stroke individuals in comparison to placebo (Supplemental Figure 2-4 and Supplemental Figure 2-5) than in non-stroke people with T2DM (Supplemental Figure 2-6 and Supplemental Figure 2-7).

In this review, the most commonly observed fractures occurred in the spine and lower limbs in patients using pioglitazone versus placebo. These findings may cast doubt on the findings of the fracture risk with post-stroke pioglitazone use. In insulin-resistant individuals with acute stroke (IRIS) [141] and in people with T2DM at a high risk for MACEs with a previous incidence of stroke/TIAs of 18.8% (PROactive) [140] it is worth noting that these events are related to multiple low energy or non-serious fractures, respectively. One might argue that individuals use their peripheral extremities to break falls and if we assume that

stroke survivors have more permanent weakness in or skeletal impairments to their peripheral extremities, it follows that they cannot adequately defend themselves from falls. Given the different biomechanics, microarchitecture, structural integrity and composition of the spine compared to other skeletal areas, the spine is more susceptible to microdamage, [148] [149] [150] [151] which may increase the risk of spinal fractures.

The crude rate of stroke is higher in males than females and this increases dramatically in individuals aged ≥65 years. [360] [361] However, strokes tend to be more severe in females, who have a one-month fatality rate of 24.7% compared to 19.7% for males. [362] We found that the incidence risk of fractures was more evident in females than in males on pioglitazone versus placebo. Also, non-serious events were higher in women than men (Supplemental Figure 2-8 and Supplemental Figure 2-9) and serious events were higher in men than women on pioglitazone versus placebo (Supplemental Figure 2-10 and Supplemental Figure 2-11). However, such findings were largely driven by the IRIS trial [141] which noticed fractures to be related to falls. These findings raise the possibility that the risk/benefit ratio may differ between males and females because of the fracture-related severity in people who have had strokes. This warrants further consideration. However, previous pioglitazone trials have not been designed to exclude chance as an explanation for the observed differences across gender. This is something that should be considered when evaluating these findings.

It remains unclear to what extent the effect of a TZD (pioglitazone) on bone metabolism is caused by the drug itself or is due to the complex effect of diabetes on bone structure. [363] For bone mesenchymal stem cells, experimental models suggest that TZDs drugs increase bone resorption (osteoclast) [169] and decrease bone formation (osteoblast), [167] thereby accelerating bone loss. [364] We found that BMD levels in pioglitazone patients show a significant decrease at the LS and hip, from 0.18 to 0.53% SMD, but not in the FN. These changes are small and may be clinically insignificant as they are less than the average annual loss of 1% in postmenopausal women. [365] However, if such a cumulative loss happened at that rate yearly, it would be of clinical importance after 5 to 10 years of cumulative exposure to pioglitazone. These findings, though, were based only on the three trials in this review in which the BMD levels and fractures risk with pioglitazone use in diabetic [351] and nondiabetic individuals [350] [352] were monitored. Thus, determining the long-term effect of pioglitazone on bone density and fractures risk is a high-priority safety question that needs to be addressed post-stroke.

The potential protective impacts of metformin or the deleterious effects of sulfonylureas on bone health and fractures are debatable. [366] To date, the available clinical data are limited and based on in *vitro* and/or in *vivo* models. [167] Metformin inhibits PPAR-γ receptors that stimulate bone formation and it inhibits bone resorption, [367] which is the inverse of the results observed from the use of TZD drugs. With sulfonylureas, there is limited evidence regarding its contribution to fractures, but hypoglycaemia is a common adverse effect that could cause fall-related fractures. [368] In our meta-analysis, there is a nonsignificant difference in the rate of fracture in patients treated with pioglitazone versus these comparators (Supplemental Figure 2-12 and Supplemental Figure 2-13).

We conducted our analyses using fixed- and random-effect models. However, except for fractures in females, low-energy, lower limbs fixed- and random-effect models, only the fixed-effect model found significant evidence of increased fracture risk with pioglitazone use. We base our conclusions on data from the fixed-effect method because there was no significant heterogeneity across subgroups detected. This approach likewise gives more weight to large studies that consider the risk differences across participants' genders, interventional doses and follow-up period lengths. Also, a higher fracture rate associated with pioglitazone use is evident in studies that have a low risk of bias compared to nonsignificant evidence of this in studies with an unclear or high risk of bias (Supplemental Figure 2-14 and Supplemental Figure 2-15), given that we have grouped them according to the quality of evidence. We found sufficient evidence to determine that pioglitazone use is associated with greater fracture risk versus placebo in females, but not in males, but not in comparison to other drugs for T2DM treatment, such as metformin or sulfonylureas. Using the GRADE score, the evidence was moderate to high quality. However, with further stratification by skeletal area or BMD values, our confidence is less certain due to either a low GRADE subgroups score for the evidence or fewer fracture events. This means the estimated risks may change as future studies are conducted.

Stroke can cause devastating disability. Many patients consider it to be worse than death. [369] The actual detected effects are modest but important. When translating these findings to recommendations for decision-making, we noticed that the validity and reliability of these results depended on the minimum and maximum magnitude of the observed risks of fracture with pioglitazone use. The fracture data from clinical trials suggest that the administration of pioglitazone for five years in 100 patients from a population similar to ours, would be expected to cause one additional fracture in three patients (non-serious (0

fewer to 2 more) and serious (0 fewer to 3 more)) versus placebo. When making patient treatment decisions, it seems reasonable to consider the trade-off between potential benefits and risks. Therefore, preventing these fracture events may not be as important as stroke or MI prevention with pioglitazone use post-stroke.

Although there have been previous meta-analyses, [160] [161] [370] there are several differences between these and this analysis. This review represents the first study to evaluate the fracture impact of pioglitazone (TZD) use versus other antidiabetic classes with or at risk for T2DM. In it, we characterised the fracture risk, including the mechanism and severity of fractures in different skeletal areas and according to the participants' gender. We also stratify our analysis to predict the impact risk of fractures across nondiabetic individuals and the T2DM population at risk or not at risk for cardiovascular disease endpoints to determine the magnitude of the impact of pioglitazone use on fractures.

It is important to acknowledge the various restrictions to the available evidence. In this review, the included studies presented a broad scope of fracture outcomes with a poverty of data on stroke within and across trials. Although PROactive trial [140] reported results on people with T2DM post-stroke as a specific subgroup, their fracture outcomes were uncertain. In this regard, the generalisability of the fracture outcome findings in this review of people with stroke may only be applicable to IRIS results. Although we analysed fracture-related severity, there was little data on fracture outcomes. The studies did not report the duration or frequency of fracture-related disability or mortality, nor the follow-up time after a stroke, fall-incidence monitoring before or after a baseline event, or baseline data on bone surrogate markers. In this regard, we could not predict the risk of recurrent fractures. The majority of studies were conducted with relatively short follow-ups and none of these inspected fractures as a primary endpoint, in which based on un-monitored fracture as an adverse event from clinical safety data. We also noticed a caveat within the included trials: the definition of fractures varied across studies, which sometimes made identifying the exact fracture skeletal location challenging. Some recorded them as leg/hip, hip/femur, hand/wrist, foot/ankle, per-person or as a multiple fracture in the same person, making it difficult to interpret them.

2.7 Conclusion

Pioglitazone use increases fracture risk, but this finding is mostly driven by data from studies comparing pioglitazone use to placebo and by an increase in women. Yet, these data may

help stroke clinicians decide whether to use pioglitazone in selected patients and may guide further post-stroke trials.

Chapter 3 New Antidiabetic Drugs and Risk of Stroke: A Systematic Review and Meta-analysis of Randomised Controlled Trials

3.1 Introduction

Diabetes is a significant independent risk factor for stroke. It also is associated with a two to fourfold increase in the risk of cardiovascular disease (CVD). [371] [372] [373] [374] Indeed, diabetes almost doubles the rate of strokes. [375] In England, Wales and Northern Ireland, it has been a contributing factor in one-in-five strokes. [14] The disease accounts for 33% of strokes globally and over 10% of early stroke recurrences in patients aged ≥65 years. [362] It is estimated that between 15% and 44% of stroke survivors have diabetes. [376] Therefore, improving glycaemia over time could prevent further hospital admissions due to diabetes, stroke and CVD.

The European [265] and American [250] guidelines for managing strokes and transient ischaemic attack (TIAs) recommend glycaemic control for primary and secondary prevention of further CVD progression. [271] [272] To reduce the risk of micro- and macro-vascular complications, the guidelines set a HbA_{1c} goal of <7%. [273] However, with such more aggressive management comes concerns regarding adverse cardiovascular outcomes, in which the frequent use of insulin along with concomitant other anti-hyperglycaemic agents induce the risks of severe hypoglycaemia that coexists with cardiovascular autonomic neuropathy, a strong risk factor of sudden death. Therefore, the major world health regulatory agencies, including the US Food and Drug Administration (FDA) [126] and the European Medicines Agency, [127] have issued guidance stating that any post-marketing studies on new antidiabetic drugs should assess the cardiovascular safety of these drugs.

In the case of stroke patients at risk for diabetes, many neuro-preventive treatments addressing hyperglycaemia have been implemented. In the thiazolidinedione class, pioglitazone [92] has been shown to reduce stroke recurrence in insulin-resistant individuals, pre-diabetics and people who have type 2 diabetes mellitus (T2DM) (hazard ratio (HR) 0.68; 95% CI 0.50−0.92) and further major cardiovascular events (HR 0.75; 95% CI 0.64−0.87). [377] Experimental and clinical studies also suggest that incretin-based drugs (dipeptidyl peptidase-4 inhibitors (DPP4-Is) and glucagon-like peptide-1 receptor agonists (GLP1-RAs)) [378] and/or (sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) may reduce stroke risk. The incretin-based drugs work via the GLP-1 receptor by directly and indirectly suppressing endogenous glucose production. [379] [380] The SGLT2-Is work via the SGLT-2 transporter to increase urinary glucose excretion, therefore ameliorating the glucotoxicity effect, improving β-cell function and decreasing insulin resistance. [381] [382] Recently, several the results of large trials of these new drugs have been published. Previous systematic

reviews and meta-analyses have explored the cardiovascular safety of these drugs but were limited by their heterogeneity in terms of population characteristics, follow-up periods, or the endpoints studied. In addition, in many cases few stroke events mentioned.

We performed a detailed review and meta-analysis to assess the effect of emerging non-insulin antidiabetic medications (DPP4-Is, GLP1-RAs and SGLT2-Is) on stroke risk and recurrence in people with T2DM. We hypothesised that the use of these agents would decrease stroke risk in this population compared to the use of placebo or other antidiabetic therapies.

3.2 Methods

We designed our review according the Preferred Reporting Items for Reviews and Meta-Analysis (PRISMA) framework [308] and the Finding What Works in Healthcare Standards for Reviews [309] to ensure we conducted a high-quality meta-analysis. The review protocol was registered and published at University of York under the registration number PROSPERO-CRD 42017067889. [383]

3.2.1 Data sources and searches

The results were independently identified by H.A. and J.M. For published randomised clinical trials (RCTs), we searched the Cochrane Central Register of Controlled Trials and Systematic Review, MEDLINE, EMBASE and Web of Science from their inception to Week 36 in 2017. The updated searched was done in Week 10 in 2020. For unpublished RCTs, we sought them by scrutinizing the ClinicalTrials.gov registries. [311] The search combined a range of medical subject headings for stroke, T2DM and currently available DPP4-Is, GLP1-RAs and SGLT2-Is agents. Each class of these antidiabetic drugs were reviewed separately (Appendices 3.1). All reviews, conferences abstracts and bibliographies of each retrieved article were additionally reviewed to identify all other relevant articles.

3.2.2 Study selection

We included all clinical trials that enrolled participants aged ≥18 years with T2DM and compared DPP4-Is, GLP1-RAs and/or SGLT2-Is with placebo or other anti-hyperglycaemic drugs that also reported stroke events. All studies were eligible regardless of their baseline characteristics, treatment dose, duration, or administration method or whether a blinding

procedure for the treatment of interest was used. Any reason for ongoing or exclusion of trials was kept (Supplemental Table 3-1 and Supplemental Table 3-2).

3.2.3 Data extraction and quality assessment

Data were extracted in a predefined form that included details on baseline characteristics of enrolled population (the duration of diabetes, HbA_{1c} levels, prior stroke or TIA, age and gender), study design and method, number of patients in treatment and control arms, the backgrounds of users or non-users of other anti-hyperglycaemic agents and duration of follow-up. This was done by H.A. The results were adjudicated by senior authors J.D. and any discrepancies were resolved by discussion or consensus.

Each included study was appraised for quality and risk of bias. The risk of bias was assessed according to the judging criteria described in the Cochrane Quality Assessment Tool for assessing bias risk in RCTs. [322] The extracted information was in a predefined form for studies that included details on methods of assessment under six main domains; selection bias, detection bias, performance bias, attrition bias and other potential sources of bias. Each domain was judged to be either 'low risk', 'high risk' or 'unclear', with the last category indicating uncertainty or lack of information. For studies with unclear or high risk, any of the first three bias domains was scored as 'high risk' were considered to have low-quality evidence.

We used the GRADE methodology to assess and grade the quality of evidence for the meta-analyses. [323] [324] This method specifies grades of trial quality (very low, low, moderate or high). The score would be 'high' if the summary included several trials with low risk. A study's score might be down-rated, however, if there were concerns about the study risk of bias, [325] imprecision, [326] inconsistency, [327] indirectness [328] and/or publication bias. [329]

3.2.4 Outcomes measures

The primary endpoint was the occurrence of any stroke. This endpoint defined either as a clinical event reported from a composite of major adverse cardiovascular events (MACEs) in trials that assessed cardiac and neurological vascular outcomes, or non-serious or serious stroke events taken from trials' clinical safety data. The secondary stroke endpoint was included non-fatal or fatal stroke events. These stroke data were reported by cause or subtype

(ischaemic or haemorrhagic), including deaths, either related to stroke clinical syndrome as a causative effect or death within 30 days consensus during surveillance of follow-up. Stroke outcomes were adjudicated by the members of independent committees in blinded fashion, as recommended by the FDA guidelines. [384] [385] All these events were defined by the standard Medical Dictionary for Regulatory Activities (version 15.0), [330] which lists cerebrovascular disorders of preferred terms for stroke types and subtypes.

3.2.5 Data synthesis (narrative review)

For data synthesis, we categorised comparator anti-hyperglycaemic drug exposure backgrounds (monotherapy or add-on therapy) by the following drugs classes: biguanide, sulfonylurea, TZDs, α-glucosidase-Is, DPP4-Is, GLP1-As, SGLT2-Is and insulin (Supplemental Table 3-3). To avoid unit-of-analyses errors, for trials with variable doses of DPP4-Is, GLP1-As, SGLT2-Is, each drug class was grouped individually to create a single pairwise comparator of the same family. In studies were patients given placebo and anti-hyperglycaemic agents were grouped together as active comparators.

In cases of multiple treatment arms, if trials with ≥2 arms were designed to evaluate simultaneously the DPP4-I and/or GLP1-RA and/or SGLT2-I class and subclasses, we excluded one or two of these class from our interventions-of-interest arm, re-reported their data separately and then compared one of them to placebo and/or other anti-hyperglycaemic agents. For studies that involved multiple follow-up periods, we collected stroke outcomes data in preference for both short and long durations regardless of whether the study participants were blind to our intervention of interest.

3.2.6 Statistical analyses

In cases where stroke was assessed in ≥2 studies, we set a summary value using pooled data for a quantitative evaluation. Using a Cochran Mantel-Haenszel test, we combined stroke risk with a continuity correction of 0.5 for studies with zero events in any one treatment arm. We calculated pooled risk ratio (RR) and 95% CIs for dichotomous outcomes. However, trials with zero events in both arms were excluded in our meta-analyses to avoid data distortions.

The meta-analysis was performed for the following outcomes: the incidence risk of strokes as non-fatal and/or fatal ischaemic or haemorrhagic strokes. To categorize the risk

of fatal stroke, we aimed to separate the cause of death from mode of death related to stroke endpoints specifically rather than causes related to other MACEs composite outcomes. Stroke events were analysed to explore the net stroke safety effects of large, published Phase IV trials among relatively small trials (Phase II or III), by non-serious or serious adverse events, for people with T2DM, for people at risk or not at risk for CVD or chronic kidney disease (CKD) endpoints at the different baseline characteristics across studies. To further explore the heterogeneity across our treatment interventions of interest (DPP4-Is, GLP-1As or SGLT2-Is), all stroke events were state to explore the collective impact of these therapies independently by class and sub-class versus placebo and the active comparators of T2DM therapies.

Fixed and random-effect models were applied independently. The fixed-effect model assumes the null hypothesis is that each study is estimated from populations with the same effect-size. This model is used when heterogeneity within meta-analyses is absent. However, to further explore the presence of unexplained heterogeneity across subgroups of meta-analyses, we used a random-effect model. [331] [332] This model assumes that different studies estimated from populations with different effect-sizes have related intervention effects. This method is based on an inverse-variance approach that makes adjustments to study weights according to the extent of heterogeneity or the variation among intervention effects.

We explored inter-study heterogeneity using a Q statistic quantified by a I^2 statistic. These indices were used to assess the variability percentage across the studies. We viewed a higher value of $I^2 \geq 75$ to indicate considerable heterogeneity [333] not due to chance. [334] We assessed potential reporting bias using an Egger linear regression [335] and a Begg rank correlation test, [336] which we visually evaluated using funnel plots. This test was constructed by plotting the study's inverse total standard error as an independent variable against the treatment-effect magnitude, including the natural log of the RRs, for each analysis as dependent variables. The plot should resemble a symmetrical inverted funnel in the absence of reporting bias.

We considered a P-value of <0.05 to be statistically significant for all outcome and heterogeneity analyses. All tests were two-sided. The RR, absolute risk (AR), absolute risk difference (ARD) and the incidence rate per 100 patient-years was calculated. We used the Review Manager [337] and GRADEpro GDT [338] software to perform the combined

statistical analyses and produce graphical output. All analyses were performed by H.A. and reviewed by J.D. and C.H.

3.3 Results

The literature search identified 960 trials. From these, 269 studies were eligible for full-text review and only 256 satisfied our eligibility criteria, following the PRISMA checklist [339] (Figure 3-1). These trials included 356,783 total participants and 3,914 stroke outcomes. The main baseline characteristics of the all selected trials is detailed in (Supplemental Table 3-4 for DPP4-1s, Supplemental Table 3-5 for GLP1-RAs and Supplemental Table 3-6 for SGLT2-Is).

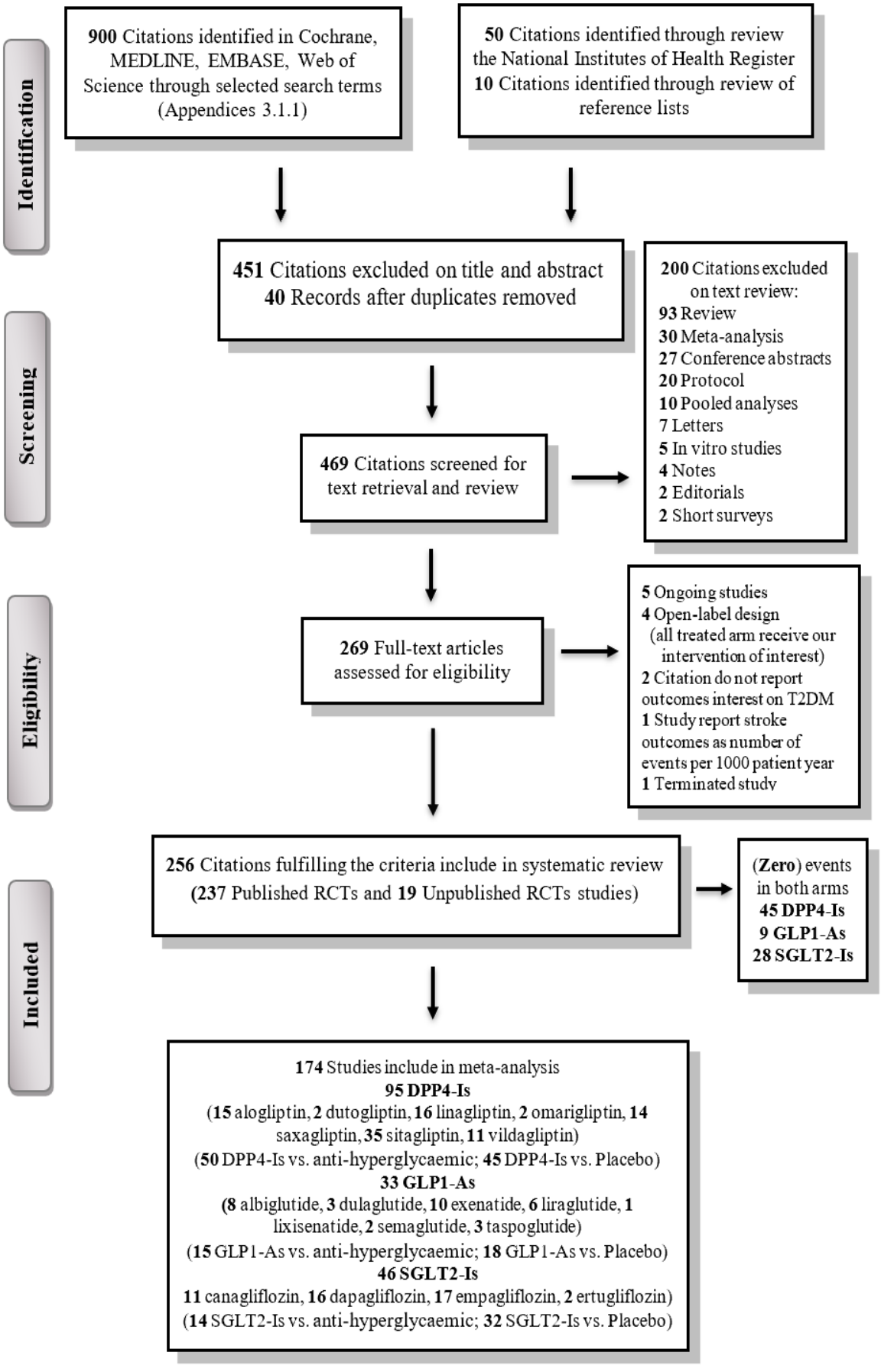

Figure 3-1. PRISMA flow chart depicting the selection process of the studies included in the systematic review and meta-analysis.

3.3.1 Study description

With respect to study blinding, 32 of the reviewed trials were of open-label design and 224 were double-blind, randomised studies.

3.3.2 Study population

Study participants had all been diagnosed with T2DM when enrolled in these studies and were either had inadequate glycaemic control despite the use of antidiabetic drugs or received no hypoglycaemic treatment. Participants were relatively young, with average age of ≤79 years and 61.5% of participants were male. Diabetes control was relatively poor, with a mean duration of ≥10 years and a mean HbA_{1c} of approximately 9%. Fifteen trials enrolled people with T2DM and established CVD (four trials with DPP4-Is and two trials with GLP1-RAs); established CVD, previous MI and coronary revascularisation (one trial with GLP1-RAs); established CVD and CKD stage III (one trial each with DPP4-Is and GLP1-RAs); established CVD, HF class II and III and CKD stage III (two trials each with SGLT2-Is and GLP1-RAs); and recent acute coronary syndrome (one trial each with DPP4-Is and GLP1-RAs). In included studies, pre-existing CVD was; prior CVD (24.9% for DPP4-Is, 71.4% for GLP1-RAs and 92.5% for SGLT2-Is), CKD (11.9% for DPP4-Is, 20.7% for GLP1-RAs and 13.9% for SGLT2-Is) and stroke/TIA (5.0% for DPP4-Is, 1.4% for GLP1-RAs and 5.5% for SGLT2-Is).

3.3.3 Study interventions and exposures

Of the total studies of DPP4-Is, 77 studies compared DDP4-Is versus placebo and 63 studies compared DDP4-Is versus active comparators. In studies compared the DPP4-Is to placebo the drugs studied were; 9 alogliptin, 2 dutogliptin, 15 linagliptin, omarigliptin, 14 saxagliptin, 25 sitagliptin and 11 vildagliptin. In studies compared the DPP4-Is versus active comparators the drugs studied were; 10 alogliptin, 8 linagliptin, omarigliptin, 8 saxagliptin, 29 sitagliptin and 7 vildagliptin.

Of the total studies of GLP1-RAs, 24 studies compared GLP1-RAs versus placebo and 18 studies compared GLP1-RAs versus active comparators. In studies comparing the GLP1-RAs to placebo the drugs studied were; 5 albiglutide, 3 dulaglutide, 6 exenatide, 2 liraglutide, lixisenatide, 2 semaglutide and 5 taspoglutide. In studies comparing the GLP1-RAs versus active comparators the drugs studied were; 5 albiglutide, 6 exenatide, 4 liraglutide and 3 taspoglutide.

Of the total studies of SGLT2-Is, 57 studies compared SGLT2-Is versus placebo and 17 studies compared SGLT2-Is versus active comparators. In studies comparing the SGLT2-Is to placebo the drugs studied were; 12 canagliflozin, 27 dapagliflozin, 14 empagliflozin, 1 ertugliflozin and 3 ipragliflozin. In studies comparing the SGLT2-Is versus active comparators the drugs studied were; 5 canagliflozin, 3 dapagliflozin, 7 empagliflozin and 2 ertugliflozin).

Most studies employed different comparative dosing therapies administered orally or by injection. Additional glucose-lowering medications were used during individual studies according to their approved dosage regimens in line with usual medical care practice. Of the total included studies, in 59 their participants were naïve to antidiabetic drugs and in 197 their participants were had been exposed to diverse T2DM treatment therapies. Trial follow-ups ranged from 4 to 432 weeks for the DPP4-I group, 12 to 339 weeks for the GLP1-RA group and 12 to 318 weeks for the SGLT2-I group.

3.3.4 Assessment risk of bias

Generally, 32 studies were scored as high risk, 19 as unclear and 205 as low risk. The quality assessment provided adequate descriptive data for random sequence generation. However, 32% of the studies had high risk for performance bias because their participants had a knowledge of received our intervention of interest before or during their study randomisation, open-label design. Selection and detection bias for these studies were scored as unclear for 19% (these studies were all unpublished RCTs). (Figure 3-2 and Supplemental Figure 3-1).

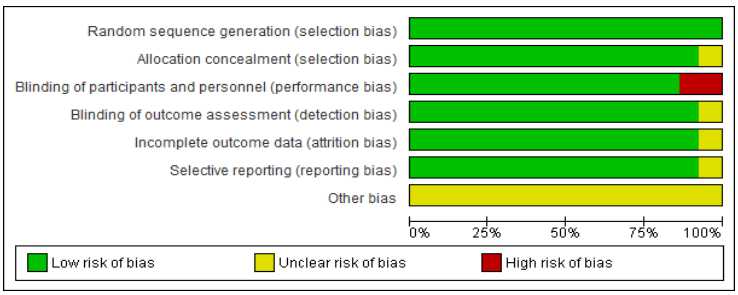

Figure 3-2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.4 Outcome measures

The characteristics of stroke outcomes of interest in each study were summarized (Supplemental Table 3-4 for DDP4-Is, Supplemental Table 3-5 for GLP1-RAs and

Supplemental Table 3-6 for SGLT2-Is). Of the total of 256 studies, no stroke events were reported in 82 studies. In 174 trials, stroke outcomes were reported.

3.4.1 DPP4-Is class

In the DPP4-Is studies, stroke by subtypes were reported as follows; ischaemic stroke in 95 trials, haemorrhagic stroke in 19 trials and fatal events in nine trials. These stroke outcomes were recorded throughout the studies as part of the safety assessment process either as a serious or non-serious stroke adverse event. The primary outcome for most of these trials was the change in HbA1c from baseline. However, seven trials designed specifically to assess MACEs outcome and included stroke events as primary or secondary outcomes.

3.4.2 GLP1-RAs class

In the GLP1-RAs studies, stroke subtypes were reported as follows; ischaemic stroke in 33 trials, haemorrhagic stroke in five trials and fatal events in seven trials. These stroke outcomes were recorded throughout the studies as part of the safety assessment process either as a serious or non-serious stroke adverse event. The primary outcome for most of these trials was the change in HbA_{1c} from baseline. However, six trials designed specifically to assess MACEs outcome and included stroke events as primary or secondary outcomes.

3.4.3 SGLT-Is class

In the SGLT2-Is studies, stroke subtypes were reported as follows; ischaemic stroke in 46 trials, haemorrhagic stroke in seven trials and fatal events in three trials. These stroke outcomes were recorded throughout the studies as part of the safety assessment process either as a serious or non-serious stroke adverse event. The primary outcome for most of these trials was the change in HbA_{1c} from baseline. However, two trials designed specifically to assess MACEs outcome and included stroke events as primary or secondary outcomes.

3.5 Outcome results

Trial outcomes results are summarized for DPP4-Is in Supplemental Table 3-7, for GLP1-RAs in Supplemental Table 3-8 and for SGLT2-Is in Supplemental Table 3-9). The meta-analysis was performed on 174 trials with at least one event (95 studies with DPP4-Is, 33 studies with GLP1-RAs and 46 studies with SGLT2-Is).

No clinically meaningful comparison differences in stroke rates in 158 studies that reports stroke outcomes as non-serious or serious events (87 for DPP4-Is, 28 for GLP1-RAs and 43 for SGLT2-Is). Most of these events were unlikely to be related to the trial interventions, in the judgement of the study investigators. However, in other 13 trials that reports stroke from the composite endpoints of MACEs the rates of stroke outcomes did not decrease significantly. Overall, the stroke magnitude differences for ischaemic or haemorrhagic events were low without a significant benefit of reduction. Of these, the following had no clinically important difference across groups or placebo: DPP4-Is (alogliptin, [386] linagliptin, [387] linagliptin, [388] omarigliptin, [389] saxagliptin, [390] sitagliptin [391]), GLP1-RAs, (albiglutide, [392] exenatide, [393] liraglutide, [394] lixisenatide, [395] semaglutide [396]) and SGLT2-Is (dapagliflozin, [397] empagliflozin [398]). In other three studies, however, a significant reduction in non-fatal stroke rates was observed with DPP4-Is (linagliptin [399]) and in MACEs rates including fatal and non-fatal strokes with GLP1-RAs (dulaglutide [400] and semaglutide [401]).

3.5.1 DPP4-Is class

The overall rate of stroke was 7% in trials where DPP4-Is were compared to non-DPP4-Is comparators. In 95 trials (109,243 participants; 1,431 stroke), the incidence of stroke with DPP4-Is was not significantly different from that versus placebo or active comparators of T2DM drugs (RR 0.93; 95% CI 0.84−1.03; P=0.14) using fixed-effect model. No differences were noted in the pooled data from random-effect model. There was no significant evidence of reporting bias or statistical heterogeneity across trials (I^2=0%). A summary table detailed the effects of the DPP4-Is class and sub-class on stroke risk (Table 3-1).

Outcome or Subgroup	Studies	Participants	Effect Estimate Mantel-Haenszel, Fixed-effect test Risk Ratio (95% confidence intervals)
1.1 Risk of stroke by subtypes and treatment allocation (DPP4-Is vs. non-DPP4-Is)	**95**	**125083**	**0.91 [0.82, 1.01]**
1.1.1 Ischaemic stroke (DPP4-Is vs. placebo)	44	65549	0.95 [0.84, 1.07]
1.1.2 Haemorrhagic stroke (DPP4-Is vs. placebo)	6	3962	0.68 [0.22, 2.12]
1.1.3 Ischaemic stroke (DPP4-Is vs. AHGs)	51	43694	0.82 [0.67, 1.01]
1.1.4 Haemorrhagic stroke (DPP4-Is vs. AHGs)	13	11878	1.28 [0.57, 2.87]
2.1 Fatal stroke risk (DPP4-Is vs. non-DPP4-Is)	**9**	**47427**	**0.93 [0.69, 1.24]**
2.1.1 Fatal ischaemic stroke (DPP4-Is vs. placebo)	3	37994	0.93 [0.67, 1.29]
2.1.2 Fatal ischaemic stroke (DPP4-Is vs. AHGs)	3	7482	0.90 [0.45, 1.79]
2.1.3 Fatal haemorrhagic stroke (DPP4-Is vs. AHGs)	3	1951	1.01 [0.20, 4.98]
3.1 Risk of stroke in T2DM by baseline characteristics (DPP4-Is vs. non-DPP4-Is)	**95**	**109243**	**0.93 [0.84, 1.03]**
3.1.1 Risk of stroke in T2DM (DPP4-Is vs. placebo)	34	17856	0.74 [0.50, 1.11]
3.1.2 Risk of stroke in T2DM (DPP4-Is vs. AHGs)	44	35102	0.75 [0.55, 1.04]
3.1.3 Risk of stroke in T2DM and CVD (DPP4-Is vs. placebo)	6	40912	1.01 [0.88, 1.16]
3.1.4 Risk of stroke in T2DM and CVD (DPP4-Is vs. AHGs)	2	6355	0.85 [0.66, 1.10]
3.1.5 Risk of stroke in T2DM and CKD (DPP4-Is vs. placebo)	5	7775	0.90 [0.67, 1.20]
3.1.6 Risk of stroke in T2DM and CKD (DPP4-Is vs. AHGs)	4	1243	1.42 [0.62, 3.25]
4.1 Risk of stroke by clinical trial size (DPP4-Is vs. non-DPP4-Is)	**95**	**109243**	**0.93 [0.84, 1.03]**
4.1.1 DPP4-Is vs. placebo (small RCTs)	40	18727	0.71 [0.49, 1.02]
4.1.2 DPP4-Is vs. placebo (large RCTs)	5	47566	1.00 [0.88, 1.13]
4.1.3 DPP4-Is vs. AHGs (small RCTs)	47	31525	0.84 [0.61, 1.15]
4.1.4 DPP4-Is vs. AHGs (large RCTs)	3	11425	0.84 [0.66, 1.08]
5.1 DPP4-Is by treatment allocation sub-class	**95**	**109243**	**0.93 [0.84, 1.03]**
5.1.1 Alogliptin vs. placebo	5	6816	0.88 [0.55, 1.41]
5.1.2 Alogliptin vs. AHGs	10	8454	0.95 [0.47, 1.91]
5.1.3 Dutogliptin vs. placebo	2	596	0.10 [0.01, 0.90]
5.1.4 Linagliptin vs. placebo	8	10112	0.89 [0.67, 1.17]
5.1.5 Linagliptin vs. AHGs	8	10749	0.80 [0.63, 1.02]
5.1.6 Omarigliptin vs. placebo	1	4192	0.94 [0.59, 1.53]
5.1.7 Omarigliptin vs. AHGs	1	642	0.20 [0.01, 4.12]
5.1.8 Saxagliptin vs. placebo	10	21163	1.08 [0.87, 1.34]
5.1.9 Saxagliptin vs. AHGs	4	3683	0.74 [0.28, 1.97]
5.1.10 Sitagliptin vs. placebo	13	20965	0.98 [0.81, 1.20]
5.1.11 Sitagliptin vs. AHGs	22	13632	1.05 [0.66, 1.67]
5.1.12 Vildagliptin vs. placebo	6	2449	0.33 [0.11, 1.04]
5.1.13 Vildagliptin vs. AHGs	5	5790	0.75 [0.32, 1.77]

Table 3-1. A summary table detailed the effects of the DPP4-Is class on the risk of stroke

3.5.1.1 DPP4-Is and non-fatal stroke by subtypes

The use of DPP4-Is did not decrease the occurrence of stroke for either ischaemic (RR 0.95; 95% CI 0.84−1.07; *P*=0.38) or haemorrhagic (RR 0.68; 95% CI 0.22−2.12; *P*=0.51) events versus placebo. The use of DPP4-Is did not decrease the occurrence of ischaemic (RR 0.82; 95% CI 0.67−1.01; *P*=0.06) or haemorrhagic (RR 1.28; 95% CI 0.57−2.87; *P*=0.54) stroke versus active comparators of T2DM drugs. (Fixed-effect (Figure 3-3) and random-effect (Figure 3-4) model). The GRADE score was moderate (Supplemental Table 3-10).

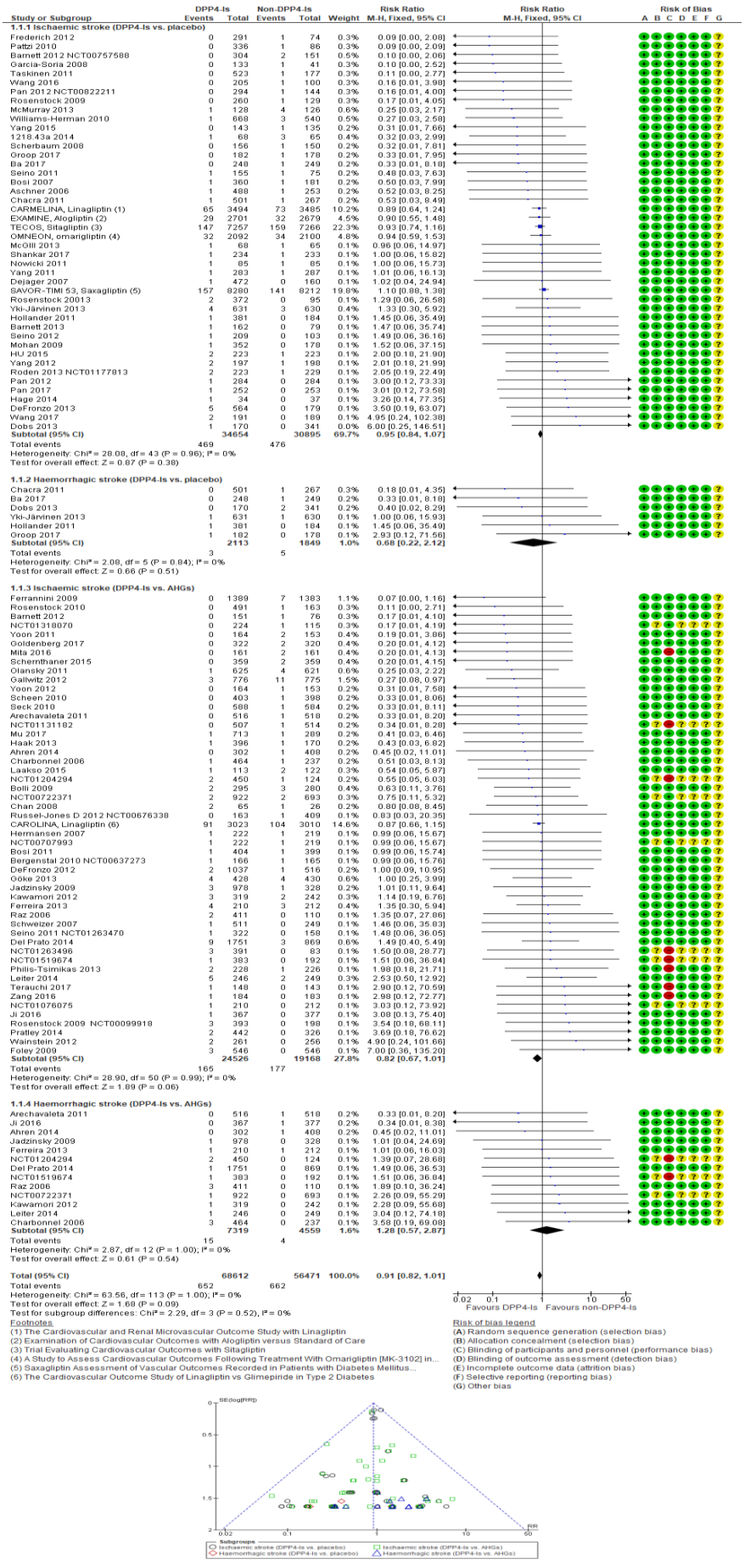

Figure 3-3. Forest and funnel plot of non-fatal stroke by subtypes with DPP4-Is therapies, Fixed-effect model.

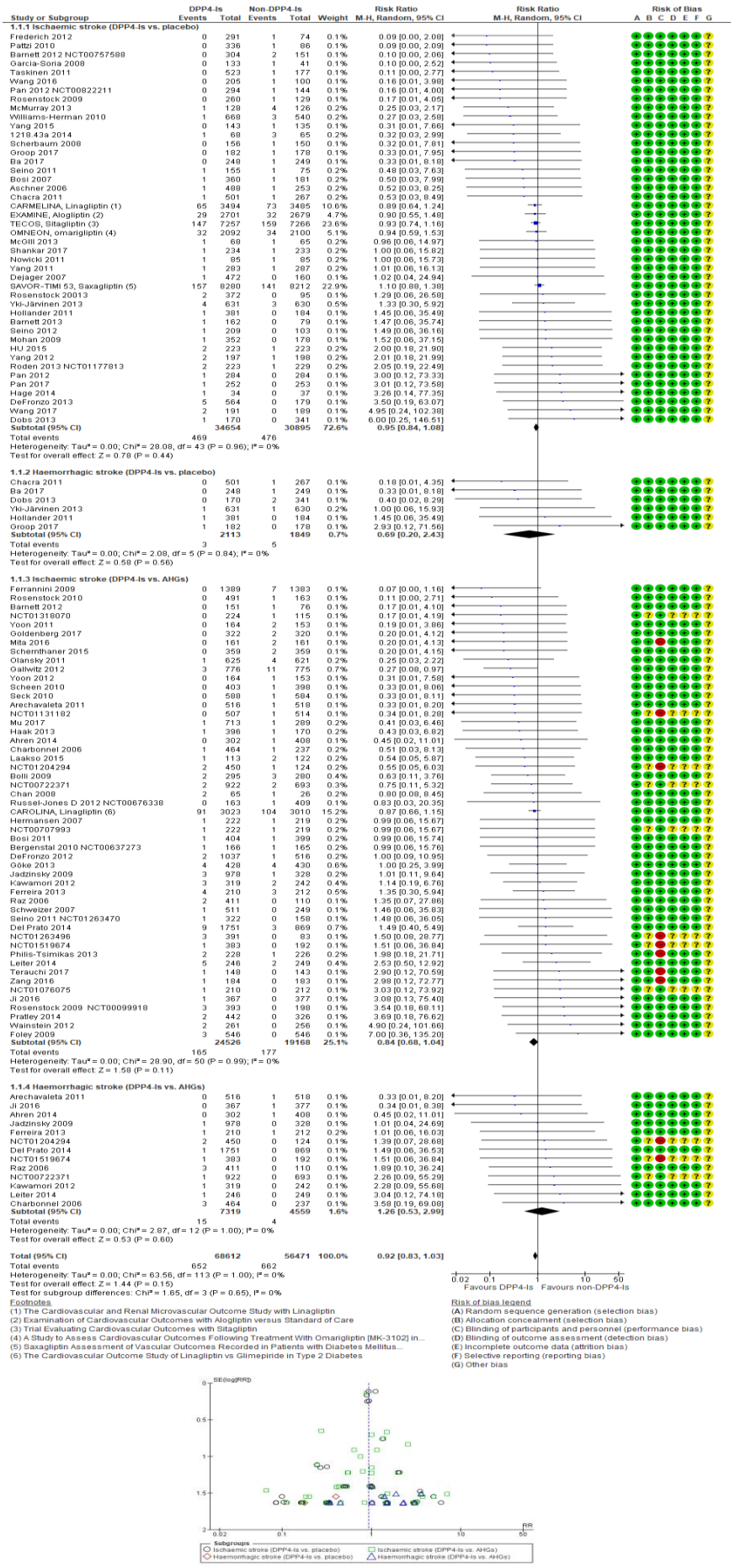

Figure 3-4. Forest and funnel plot of non-fatal stroke by subtypes with DPP4-Is therapies, Random-effect model.

3.5.1.2 DPP4-Is and fatal stroke

In nine trials (47,427 participants; 180 stroke), DPP4-Is did not decrease the risk of fatal ischaemic or haemorrhagic stroke (RR 0.93; 95% CI 0.69−1.24; *P*=0.61) versus non-DPP4-Is using fixed-effect (Figure 3-5) and random-effect (Figure 3-6) model. The GRADE score was low (Supplemental Table 3-11).

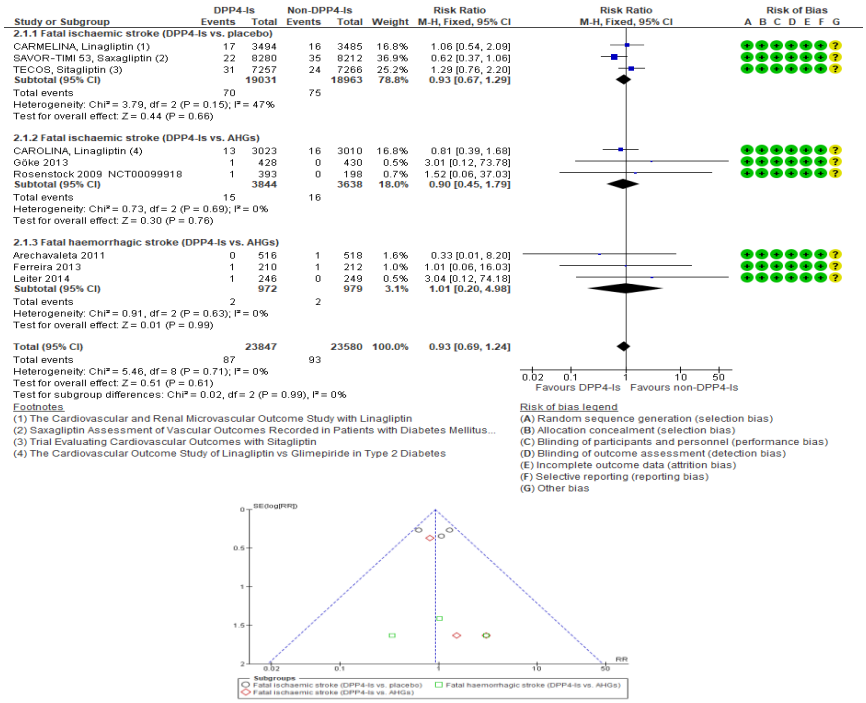

Figure 3-5. Forest and funnel plot of fatal stroke with DPP4-Is therapies, Fixed-effect model.

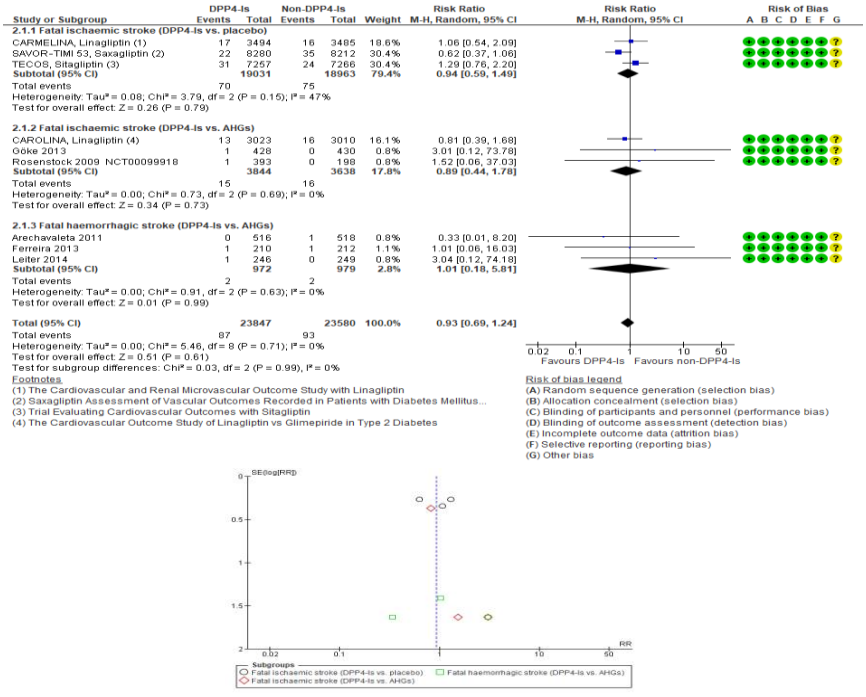

Figure 3-6. Forest and funnel plot of fatal stroke with DPP4-Is therapies, Random-effect model.

3.5.1.3 DPP4-Is and stroke by baseline characteristics

The use of DPP4-Is did not decrease stroke risk in people with T2DM at risk of CVD or CKD endpoints (RR 0.93; 95% CI 0.84−1.03; *P*=0.14) versus non-DPP4-Is using fixed-effect (Figure 3-7) and random-effect (Figure 3-8) model. The GRADE score was moderate (Supplemental Table 3-12).

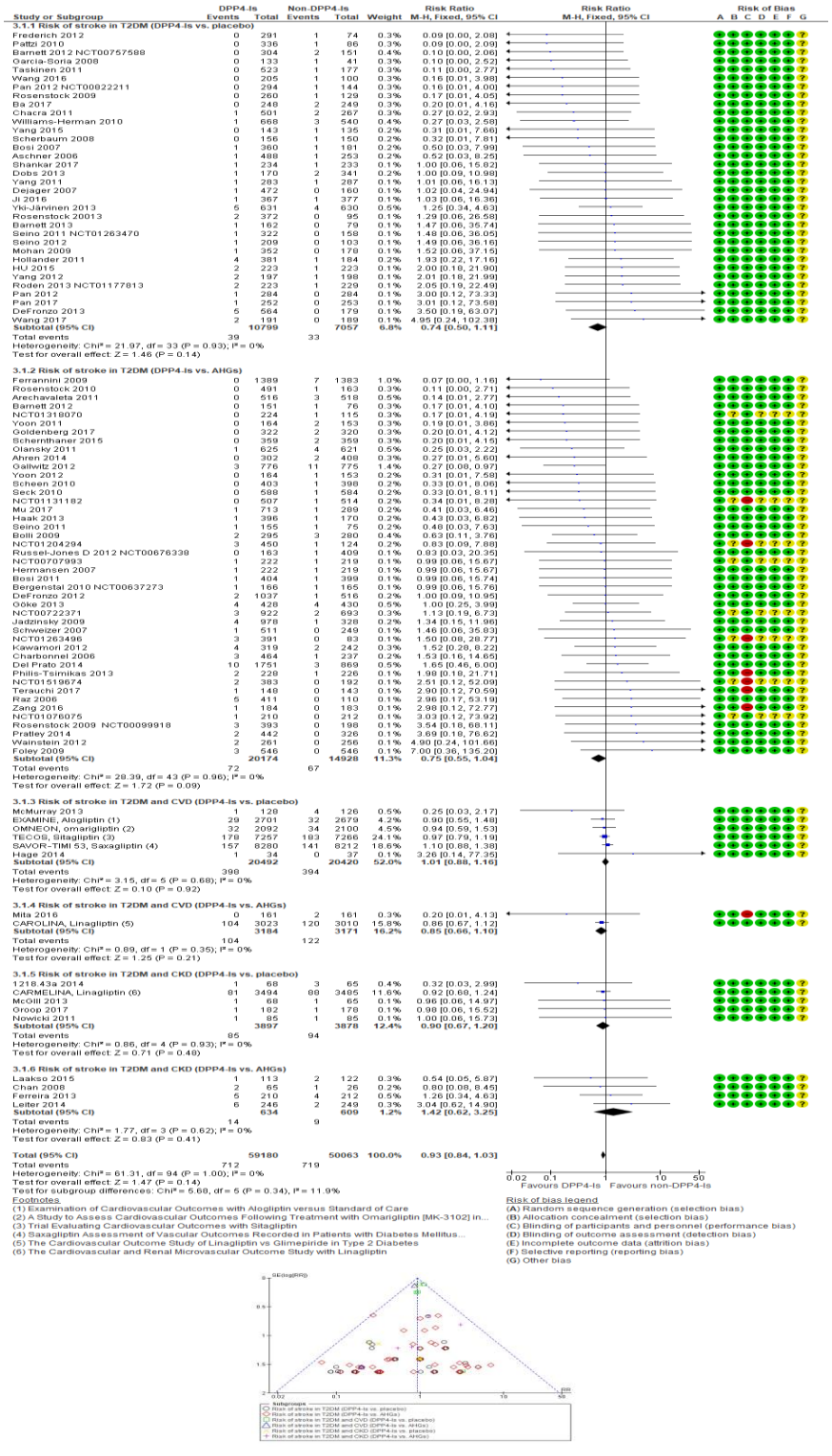

Figure 3-7. Forest and funnel plot of stroke by studies baseline characteristics with DPP4-Is therapies, Fixed-effect model.

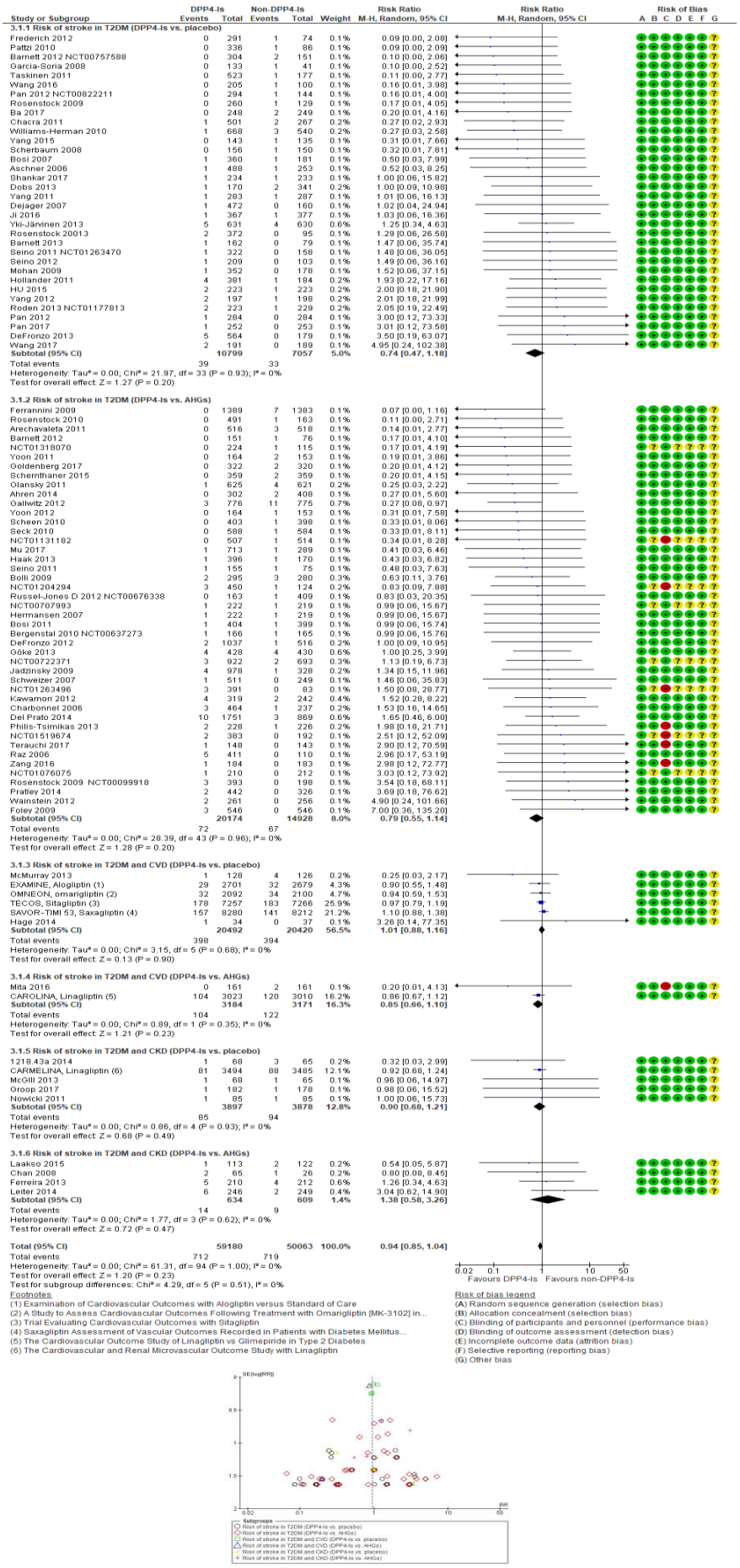

Figure 3-8. Forest and funnel plot of stroke by studies baseline characteristics with DPP4-Is therapies, Fixed-effect model.

3.5.1.4 DPP4-Is and stroke by clinical trial size

The use of DPP4-Is did not decrease stroke risk from the pooled analysis of the small RCTs (RR 0.71; 95% CI 0.49−1.02; *P*=0.07) or large RCTs (RR 1.00; 95% CI 0.88−1.13; *P*=0.94) versus placebo or in small RCTs (RR 0.84; 95% CI 0.61−1.15; *P*=0.27) or in large RCTs (RR 0.84; 95% CI 0.66−1.08; *P*=0.17) versus active comparators of T2DM drugs using fixed-effect (Figure 3-9) and random-effect (Figure 3-10) model. The GRADE score was moderate (Supplemental Table 3-13).

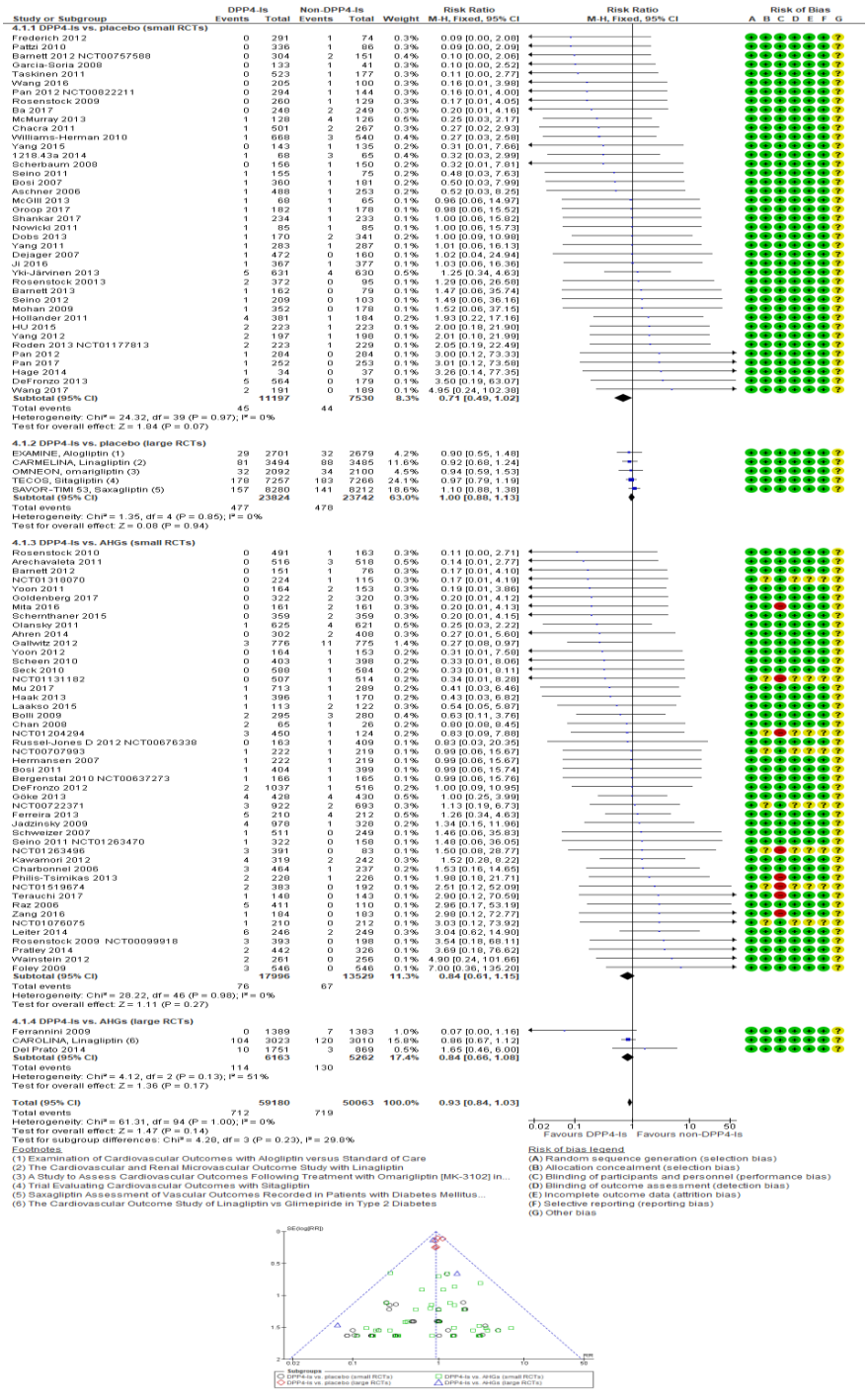

Figure 3-9. Forest and funnel plot of stroke by clinical trial size with DPP4-Is therapies, Fixed-effect model.

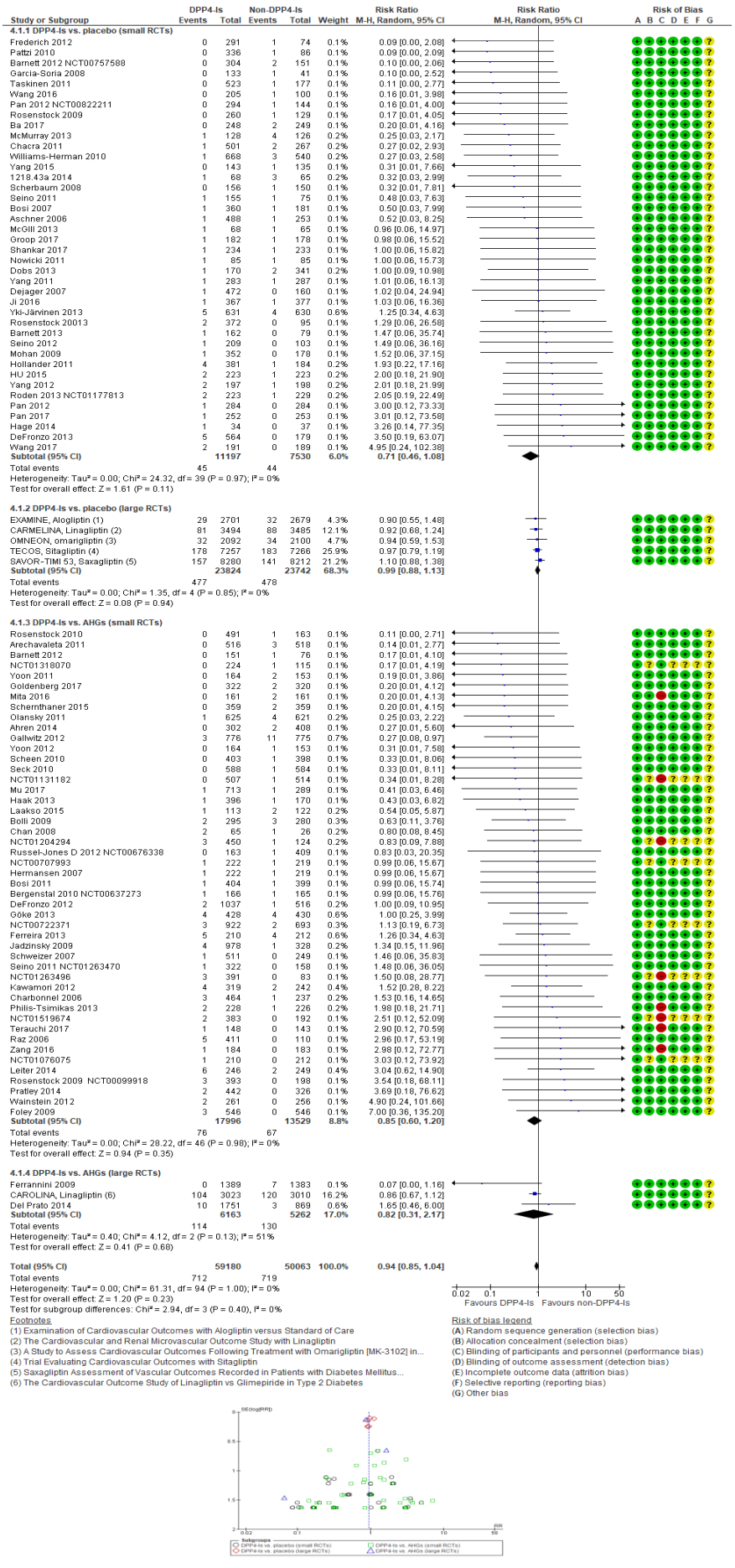

Figure 3-10. Forest and funnel plot of stroke by clinical trial size with DPP4-Is therapies, Random-effect model.

3.5.1.5 DPP4-Is and stroke by the type of DPP4-Is treatment allocation sub-class stratification

The use of DPP4-Is dutogliptin reduced stroke risk (RR 0.10; 95% CI 0.01−0.09; *P*=0.04) versus placebo. However, the use of other DDP4-Is subclasses (alogliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin and vildagliptin) did not decrease stroke risk versus placebo or active comparators of T2DM drugs. (Fixed-effect (Figure 3-11) and random-effect (Figure 3-12) model). The GRADE score was moderate (Supplemental Table 3-14).

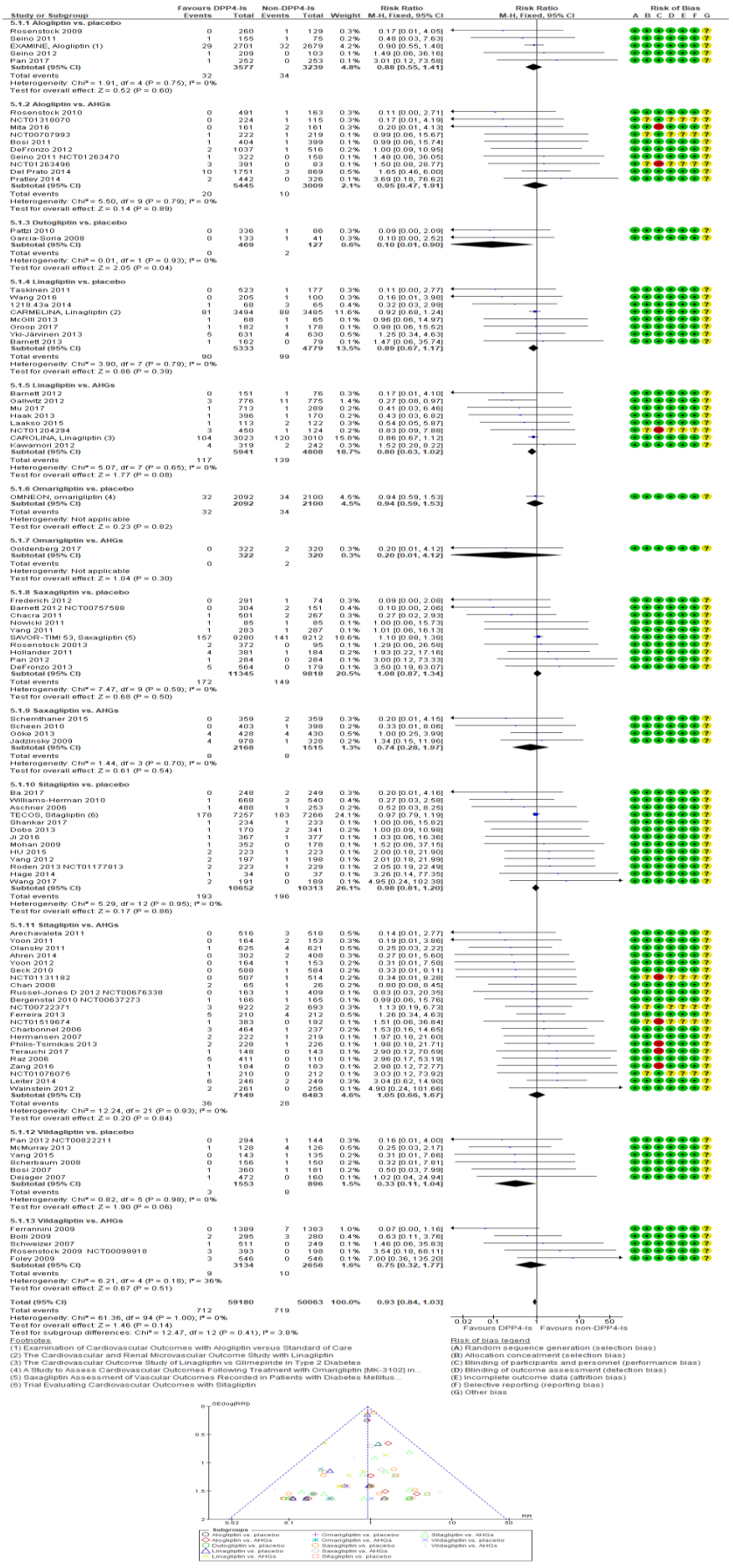

Figure 3-11. Forest and funnel plot of DPP4-Is and stroke by DPP4-Is treatment allocation sub-class, Fixed-effect model.

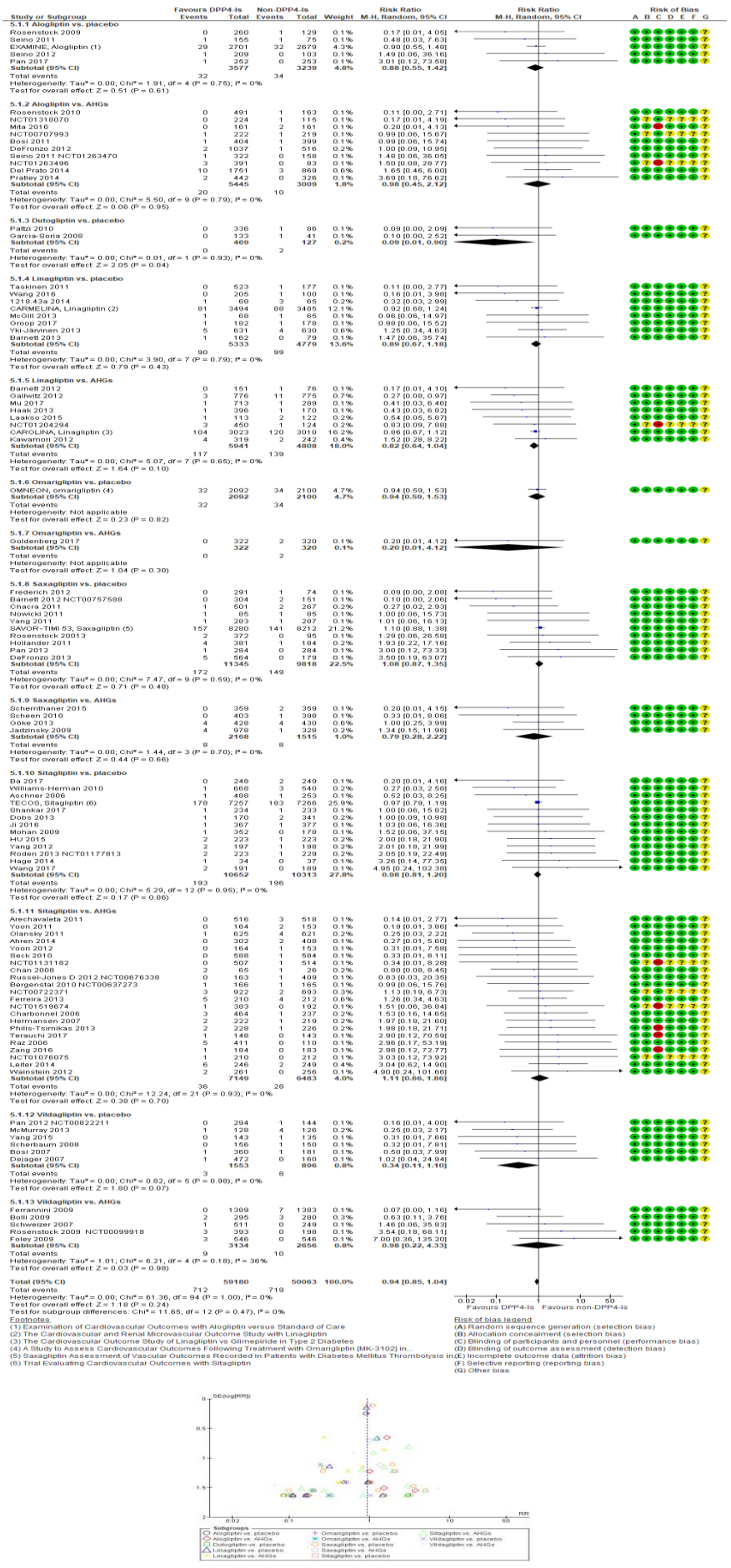

Figure 3-12. Forest and funnel plot of DPP4-Is and stroke by DPP4-Is treatment allocation sub-class, Random-effect model.

3.5.2 GLP1-RAs class

The overall rate of stroke was 16% in trials where GLP1-RAs were compared to non-GLP1-RAs comparators. In 33 trials (70,443 participants; 1,637 stroke), the incidence of stroke with GLP1-RAs was significantly decrease versus placebo or active comparator of T2DM drugs (RR 0.84; 95% CI 0.77−0.93; *P*=0.0005) using fixed-effect and random-effect model. There was no significant evidence of reporting bias or statistical heterogeneity across trials (I^2=0%). A summary table detailed the effects of the GLP1-RAs class and sub-class on stroke risk (Table 3-2).

Outcome or Subgroup	Studies	Participants	Effect Estimate Mantel-Haenszel, Fixed-effect test Risk Ratio (95% confidence intervals)
6.1 Risk of stroke by subtypes and treatment allocation (GLP1-RAs vs. non GLP1-RAs)	**33**	**76843**	**0.85 [0.77, 0.9**4]
6.1.1 Ischaemic stroke (GLP1-RAs vs. placebo)	18	59696	0.85 [0.77, 0.95]
6.1.2 Haemorrhagic stroke (GLP1-RAs vs. placebo)	1	3297	0.50 [0.09, 2.73]
6.1.3 Ischaemic stroke (GLP1-RAs vs. AHGs)	15	10747	0.80 [0.45, 1.44]
6.1.4 Haemorrhagic stroke (GLP1-RAs vs. AHGs)	4	3103	1.66 [0.41, 6.73]
7.1 Fatal stroke risk (GLP1-RAs vs. non-GLP1-RAs)	**7**	**46097**	**0.77 [0.58, 1.03]**
7.1.1 Ischaemic stroke (GLP1-RAs vs. placebo)	4	43456	0.78 [0.58, 1.05]
7.1.2 Ischaemic stroke (GLP1-RAs vs. AHGs)	1	911	0.33 [0.01, 7.97]
7.1.3 Haemorrhagic stroke (GLP1-RAs vs. AHGs)	2	1730	0.69 [0.08, 5.69]
8.1 Risk of stroke by in T2DM by baseline characteristics (GLP1-RAs vs. non-GLP1-RAs)	**33**	**70443**	**0.84 [0.77, 0.93]**
8.1.1 Risk of stroke in T2DM (GLP1-RAs vs. placebo)	11	3692	0.72 [0.36, 1.42]
8.1.2 Risk of stroke in T2DM (GLP1-RAs vs. AHGs)	15	10747	0.85 [0.48, 1.49]
8.1.3 Risk of stroke in T2DM and CVD (GLP1-RAs vs. placebo)	4	40184	0.86 [0.76, 0.96]
8.1.4 Risk of stroke in T2DM, CVD and CKD (GLP1-RAs vs. placebo)	3	15820	0.82 [0.69, 0.98]
9.1 Risk of stroke by clinical trial size (GLP1-RAs vs. non-GLP1-RAs)	**33**	**70443**	**0.84 [0.77, 0.93]**
9.1.1 GLP1-RAs vs. placebo (small RCTs)	11	3692	0.72 [0.36, 1.42]
9.1.2 GLP1-RAs vs. placebo (large RCTs)	7	56004	0.85 [0.77, 0.93]
9.1.3 GLP1-RAs vs. AHGs (small RCTs)	15	10747	0.85 [0.48, 1.49]
10.1 GLP1-RAs by treatment allocation sub-class	**33**	**70443**	**0.84 [0.77, 0.93]**
10.1.1 Albiglutide vs. placebo	4	10366	0.83 [0.64, 1.09]
10.1.2 Albiglutide vs. AHGs	4	2930	1.07 [0.44, 2.61]
10.1.3 Dulaglutide vs. placebo	3	10901	0.79 [0.64, 0.96]
10.1.4 Exenatide vs. placebo	4	15625	0.86 [0.71, 1.04]
10.1.5 Exenatide vs. AHGs	6	4156	0.93 [0.32, 2.71]
10.1.6 Liraglutide vs. placebo	2	9597	0.87 [0.71, 1.06]
10.1.7 Liraglutide vs. AHGs	4	2488	0.44 [0.14, 1.34]
10.1.8 Lixisenatide vs. placebo	1	6068	1.12 [0.79, 1.58]
10.1.9 Semaglutide vs. placebo	2	6480	0.65 [0.44, 0.97]
10.1.10 Tspoglutide vs. placebo	2	659	0.40 [0.05, 2.99]
10.1.11 Tspoglutide vs. AHGs	1	1173	2.45 [0.12, 50.83]

Table 3-2. A summary table detailed the effects of the GLP1-RAs class on the risk of stroke

3.5.2.1 GLP1-RAs and non-fatal stroke by subtypes

The use of GLP1-RAs did decrease the occurrence of ischaemic stroke (RR 0.85; 95% CI 0.77−0.94; *P*=0.002) versus placebo. However, the incidence of haemorrhagic stroke did not decrease (RR 0.50; 95% CI 0.09−2.73; *P*=0.42) versus placebo or for either ischaemic (RR 0.80; 95% CI 0.45−1.44; *P*=0.46) or haemorrhagic (RR 1.66; 95% CI 0.41−6.73; *P*=0.48) events versus active comparators of T2DM drugs. (Fixed-effect (Figure 3-13) and random-effect (Figure 3-14) model). The GRADE score was moderate (Supplemental Table 3-16).

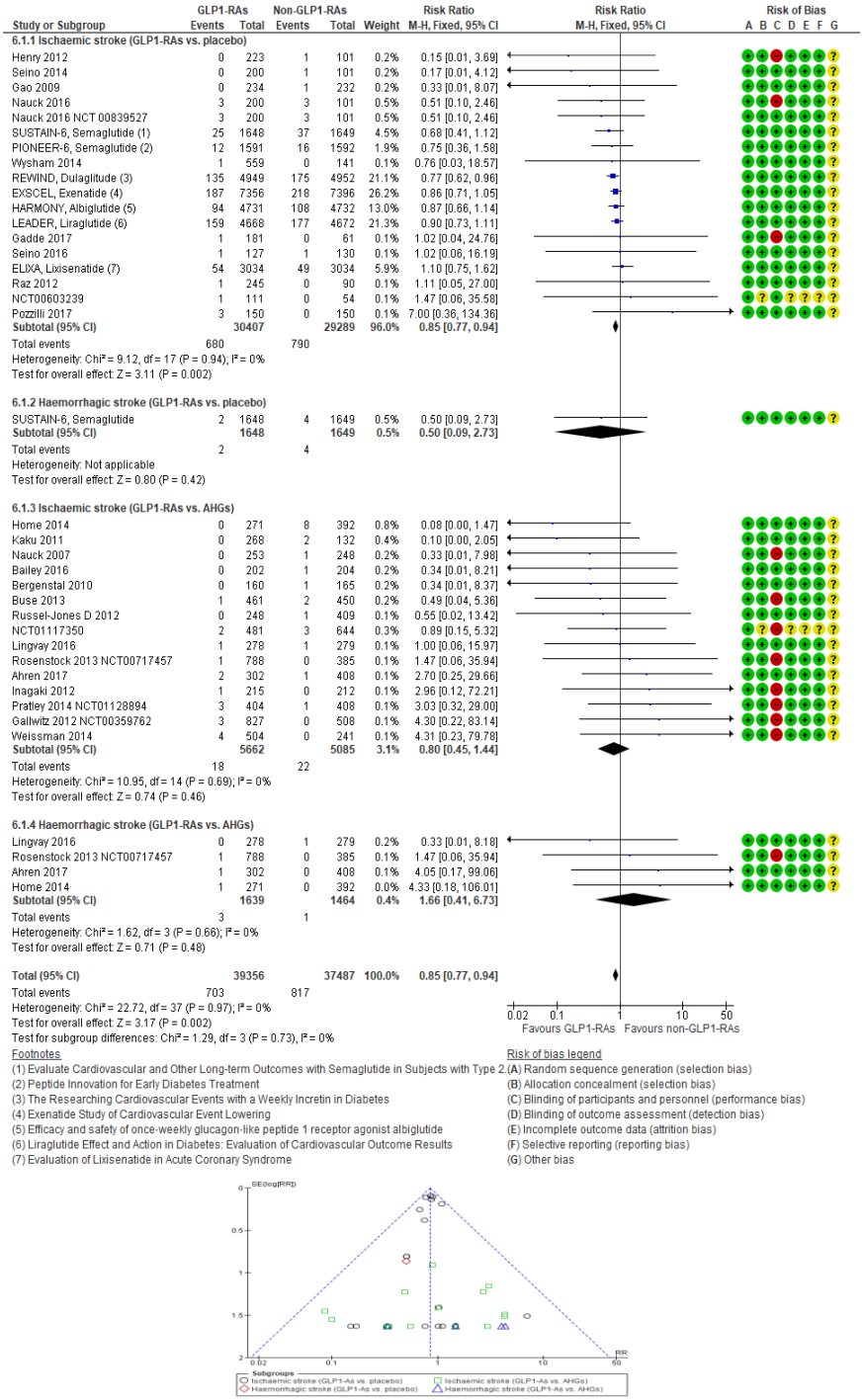

Figure 3-13. Forest and funnel plot of non-fatal stroke by subtypes with GLP1-RAs therapies, Fixed-effect model.

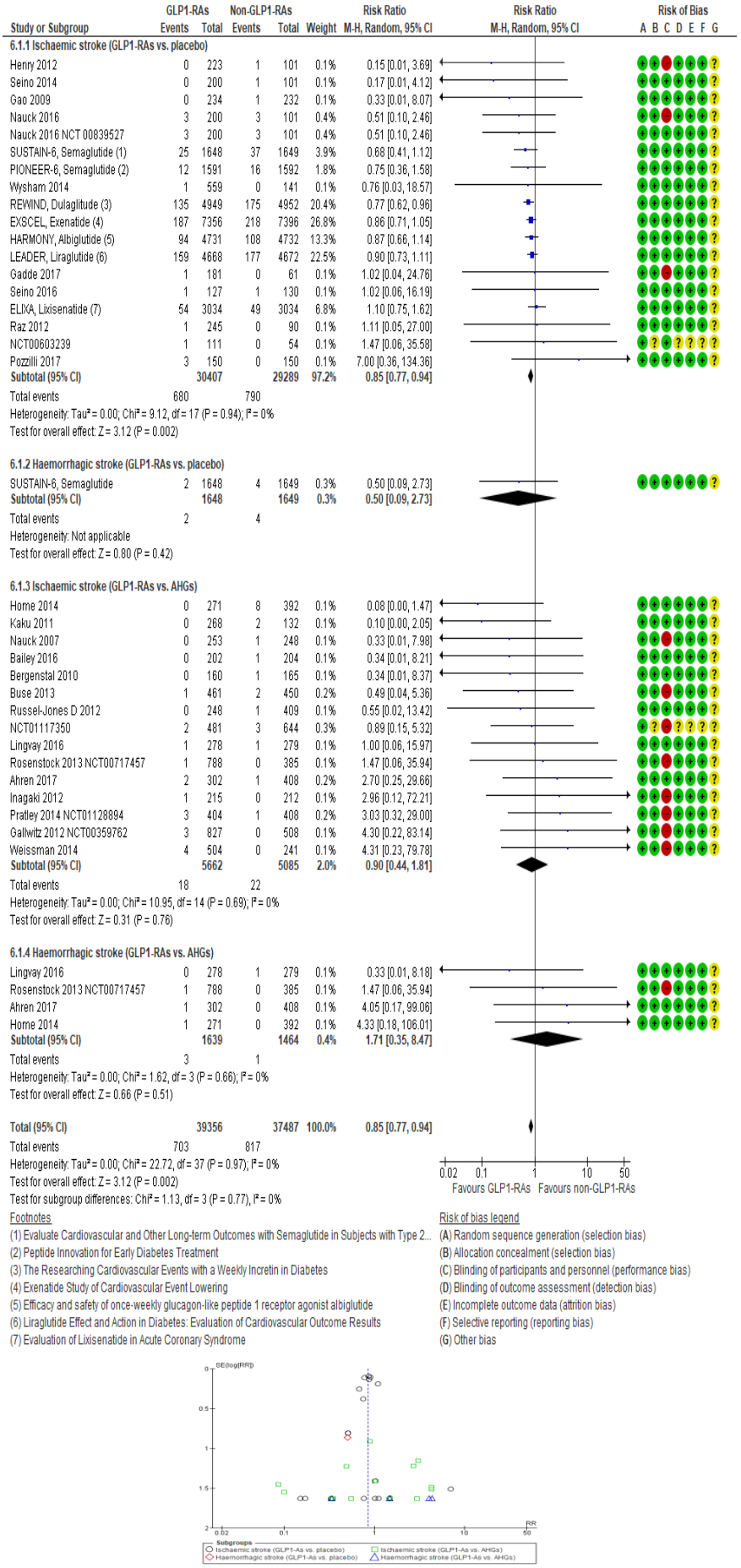

Figure 3-14. Forest and funnel plot of non-fatal stroke by subtypes with GLP1-RAs therapies, Random-effect model.

3.5.2.2 GLP1-RAs and fatal stroke risk

In seven trials (46,097 participants; 181 stroke), GLP1-RAs did not reduce the risk of fatal ischaemic or haemorrhagic stroke (RR 0.77; 95% CI 0.58−1.03; *P*=0.08) versus non-GLP1-RAs using fixed-effect (Figure 3-15) and random-effect (Figure 3-16) model. The GRADE score was very low (Supplemental Table 3-17).

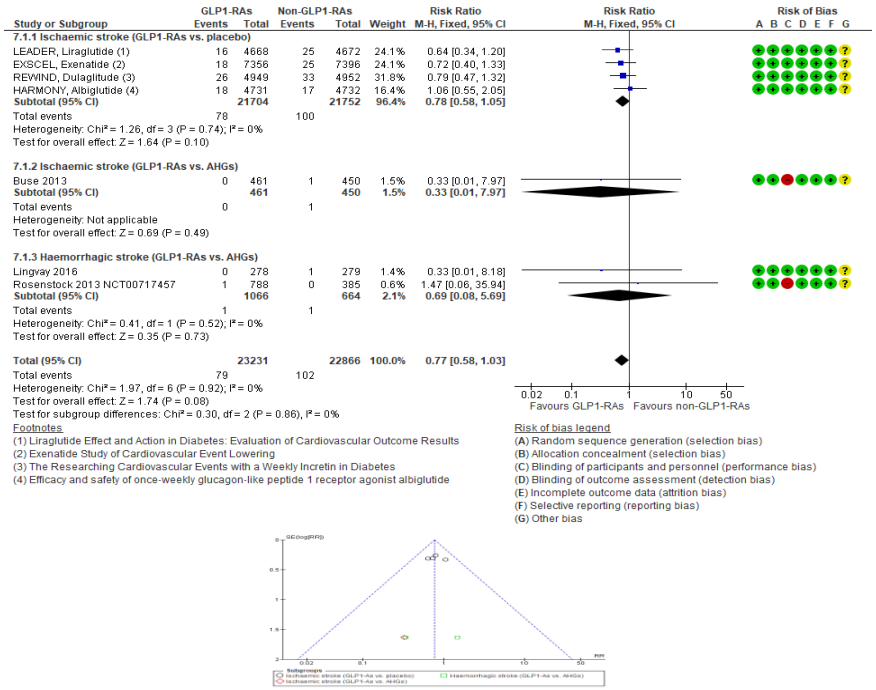

Figure 3-15. Forest and funnel plot of fatal stroke with GLP1-RAs therapies, Fixed-effect model.

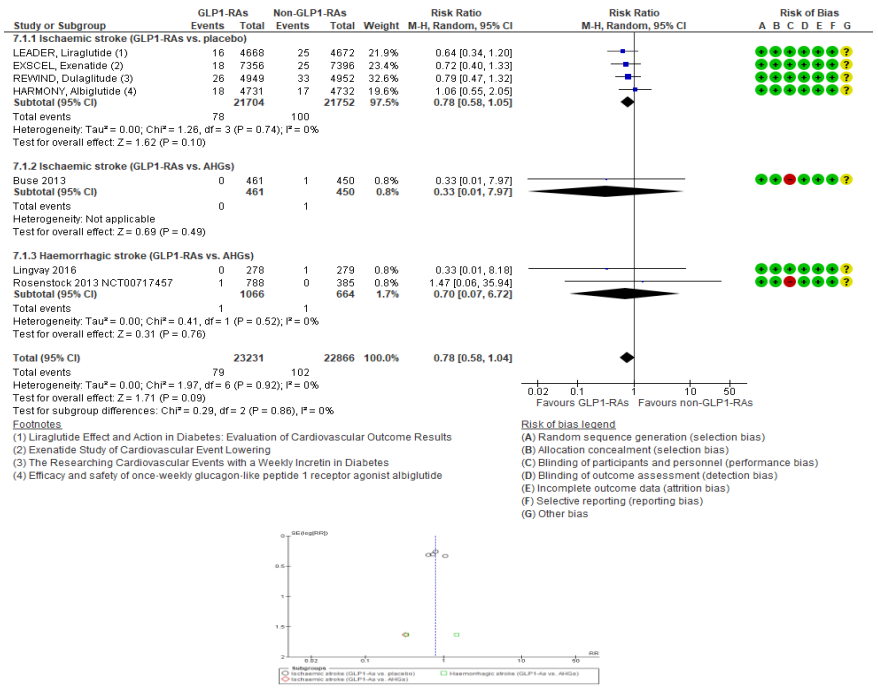

Figure 3-16. Forest and funnel plot of fatal stroke with DPP4-Is therapies, Random-effect model.

3.5.2.3 GLP1-RAs by baseline characteristics

The use of GLP1-RAs did decrease stroke risk in people with T2DM at risk of CVD endpoints (RR 0.86; 95% CI 0.76−0.96; *P*=0.01) or in people with T2DM at risk of CVD and/or CKD endpoints (RR 0.82; 95% CI 0.69−0.98; *P*=0.03) versus placebo. However, the use of GLP1-RAs did not decrease stroke risk in people with T2DM (RR 0.72; 95% CI 0.36−1.42; *P*=0.34) versus placebo or active comparators of T2DM drugs (RR 0.85; 95% CI 0.48−1.49; *P*=0.56). (Fixed-effect (Figure 3-17) and random-effect (Figure 3-18) model). The GRADE score was moderate (Supplemental Table 3-18).

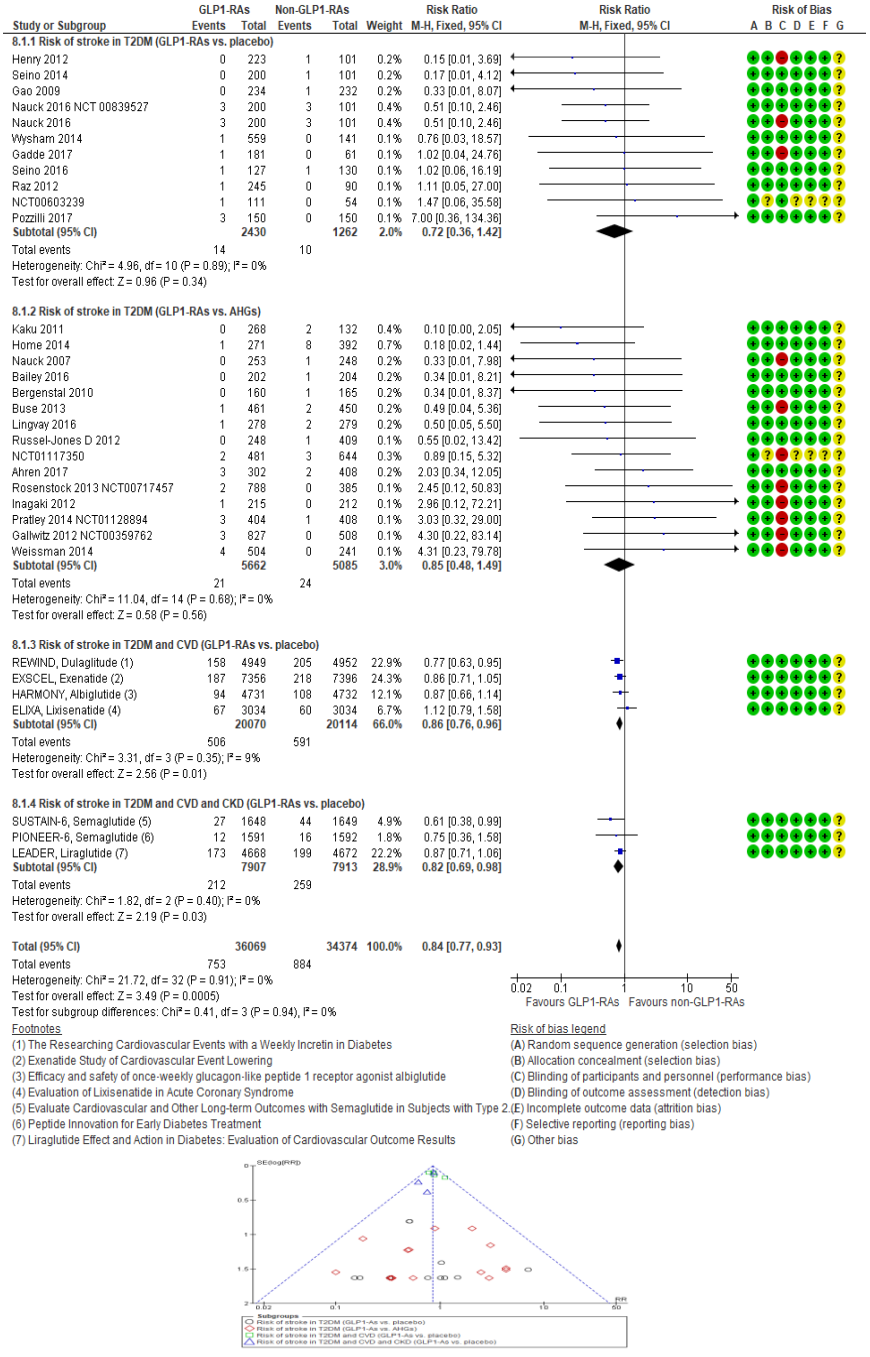

Figure 3-17. Forest and funnel plot of stroke by studies baseline characteristics with GLP1-RAs therapies, Fixed-effect model.

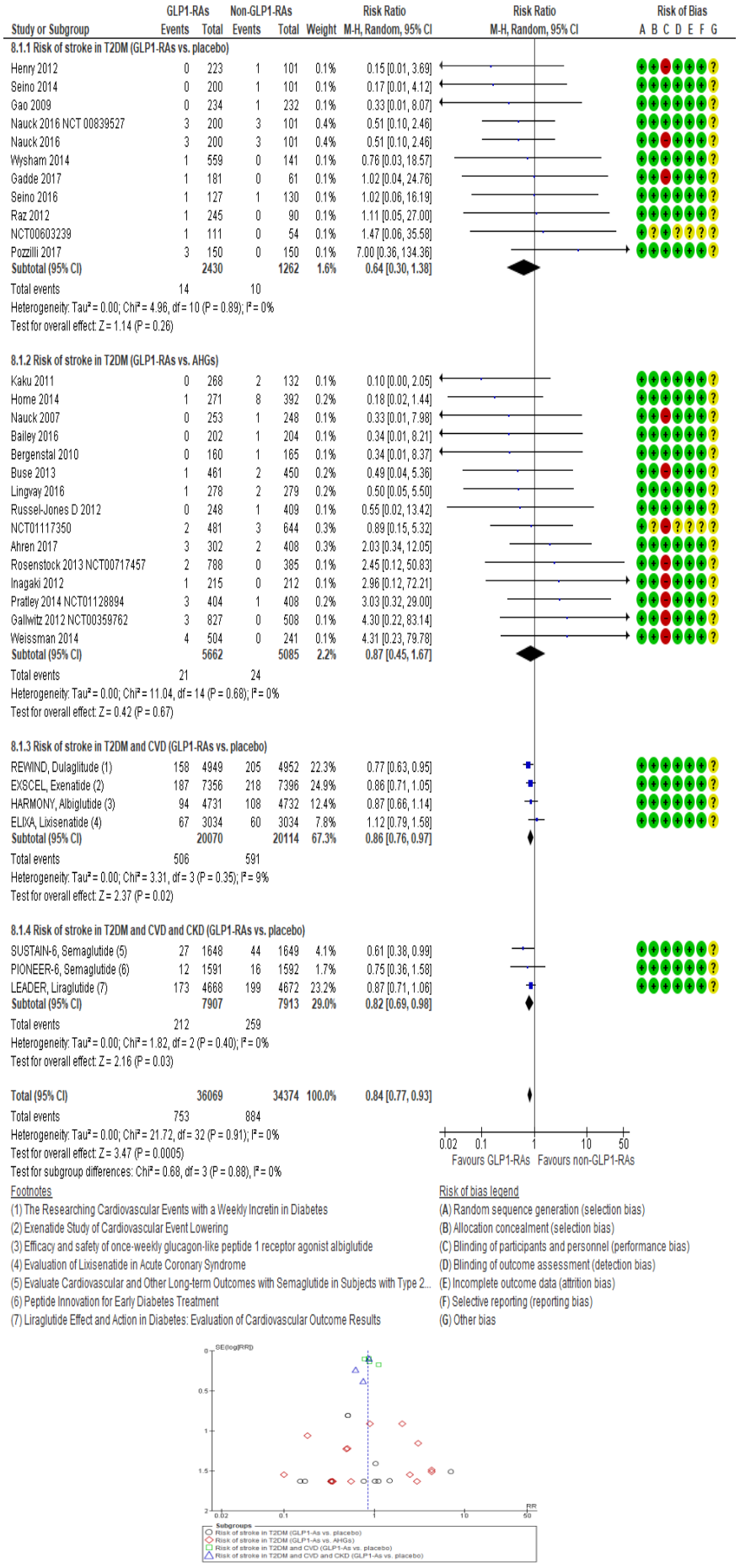

Figure 3-18. Forest and funnel plot of stroke by studies baseline characteristics with GLP1-RAs therapies, Random-effect model.

3.5.2.4 GLP1-RAs by clinical trial size

The use of GLP1-RAs did reduce stroke risk (RR 0.85; 95% CI 0.77−0.93; *P*=0.0008) from the pooled analysis of the large RCTs (RR 0.85; 95% CI 0.77−0.93; *P*=0.0008) versus placebo. In small RCTs, however, the use of GLP1-RAs did not decrease stroke risk versus placebo (RR 0.72; 95% CI 0.36−1.42; *P*=0.34) or active comparators of T2DM drugs (RR 0.85; 95% CI 0.48−1.49; *P*=0.56). (Fixed-effect (Figure 3-19) and random-effect (Figure 3-20) model). The GRADE score was moderate (Supplemental Table 3-19).

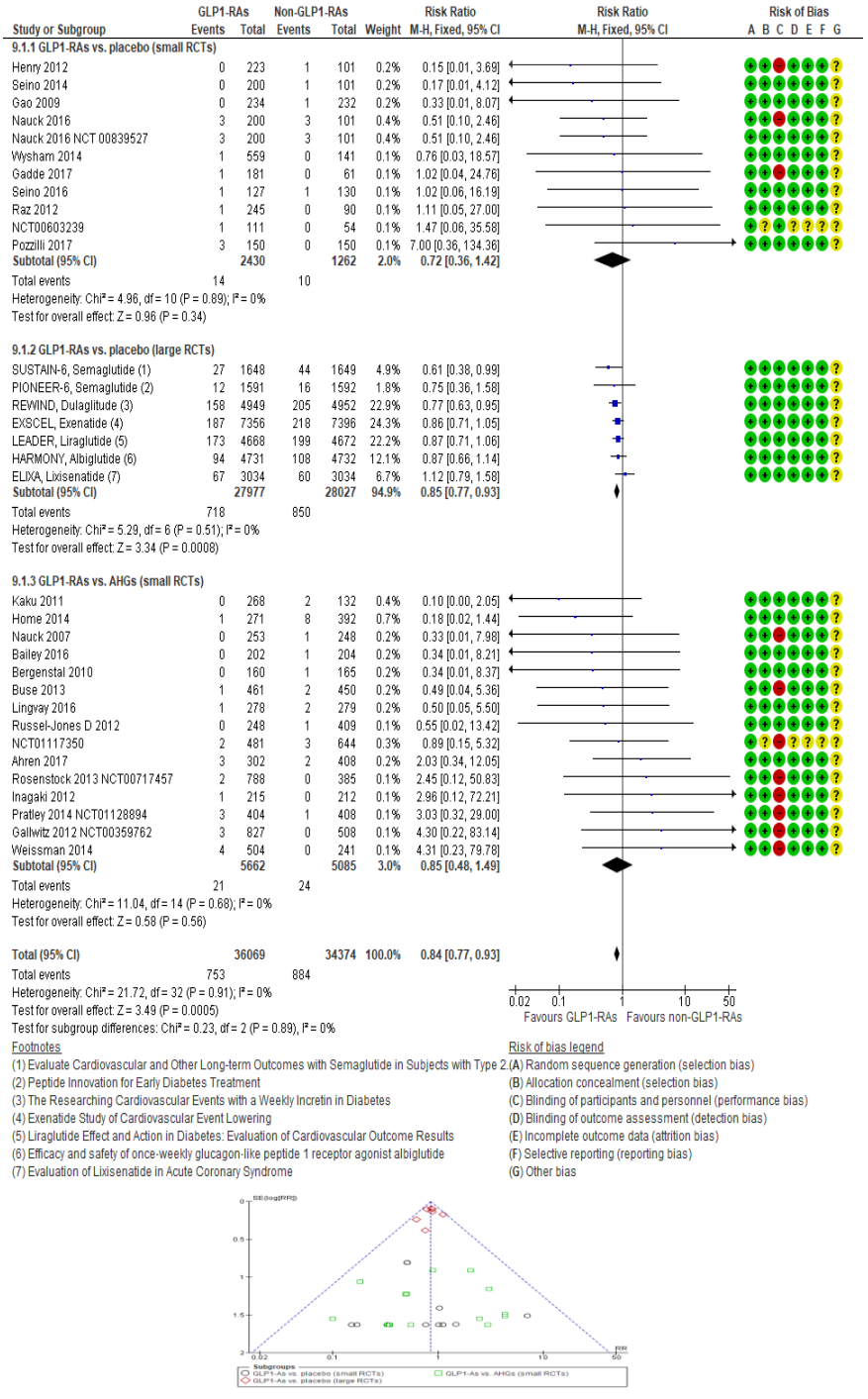

Figure 3-19. Forest and funnel plot of stroke by clinical trial size with GLP1-RAs therapies, Fixed-effect model.

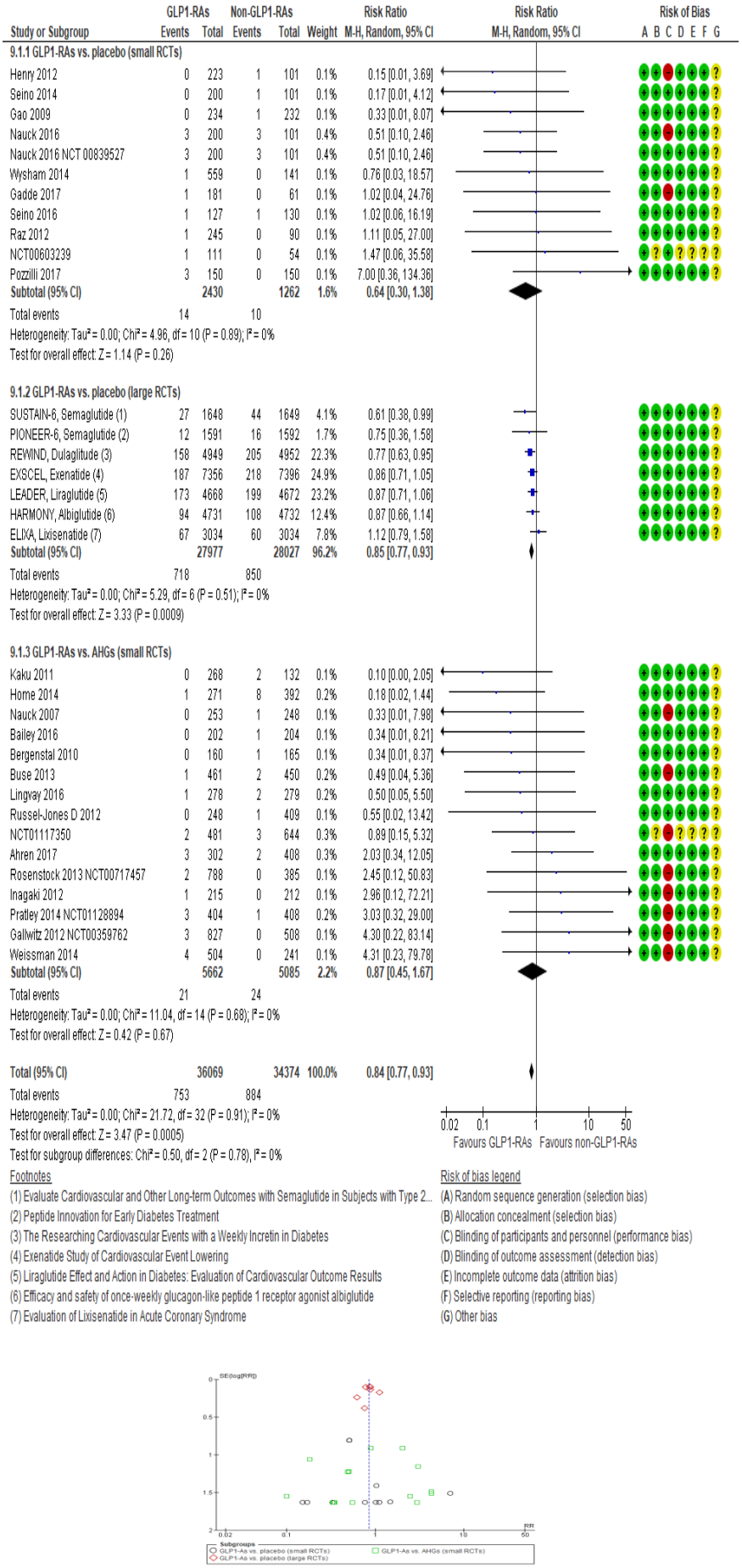

Figure 3-20. Forest and funnel plot of stroke by clinical trial size with GLP1-RAs therapies, Random-effect model.

3.5.2.5 GLP1-RAs and stroke by the type of GLP1-RAs treatment allocation sub-class stratification

The use of GLP1-RAs dulaglutide (RR 0.79; 95% CI 0.64−0.96; *P*=0.02) and semaglutide (RR 0.65; 95% CI 0.44−0.97; *P*=0.03) reduced stroke risk versus placebo. However, the use of other GLP1-RAs sub-class (albiglutide, exenatide, liraglutide, lixisenatide and taspoglutide) did not decrease stroke risk versus placebo or active comparators of T2DM drugs. (Fixed-effect (Figure 3-21) and random-effect (Figure 3-22) model). The GRADE score was moderate (Supplemental Table 3-20).

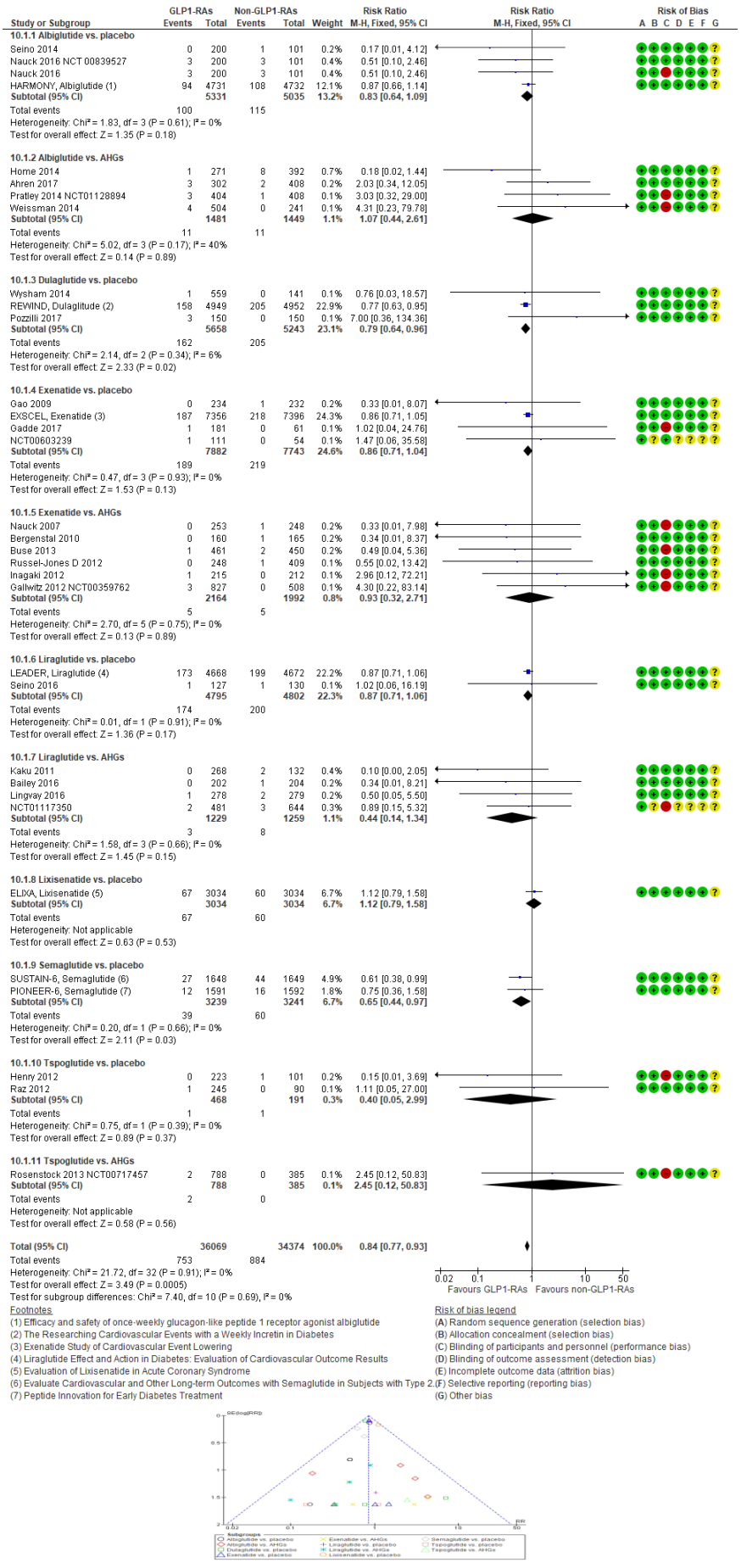

Figure 3-21. Forest and funnel plot of GLP1-RAs and stroke by GLP1-RAs treatment allocation sub-class, Fixed-effect model.

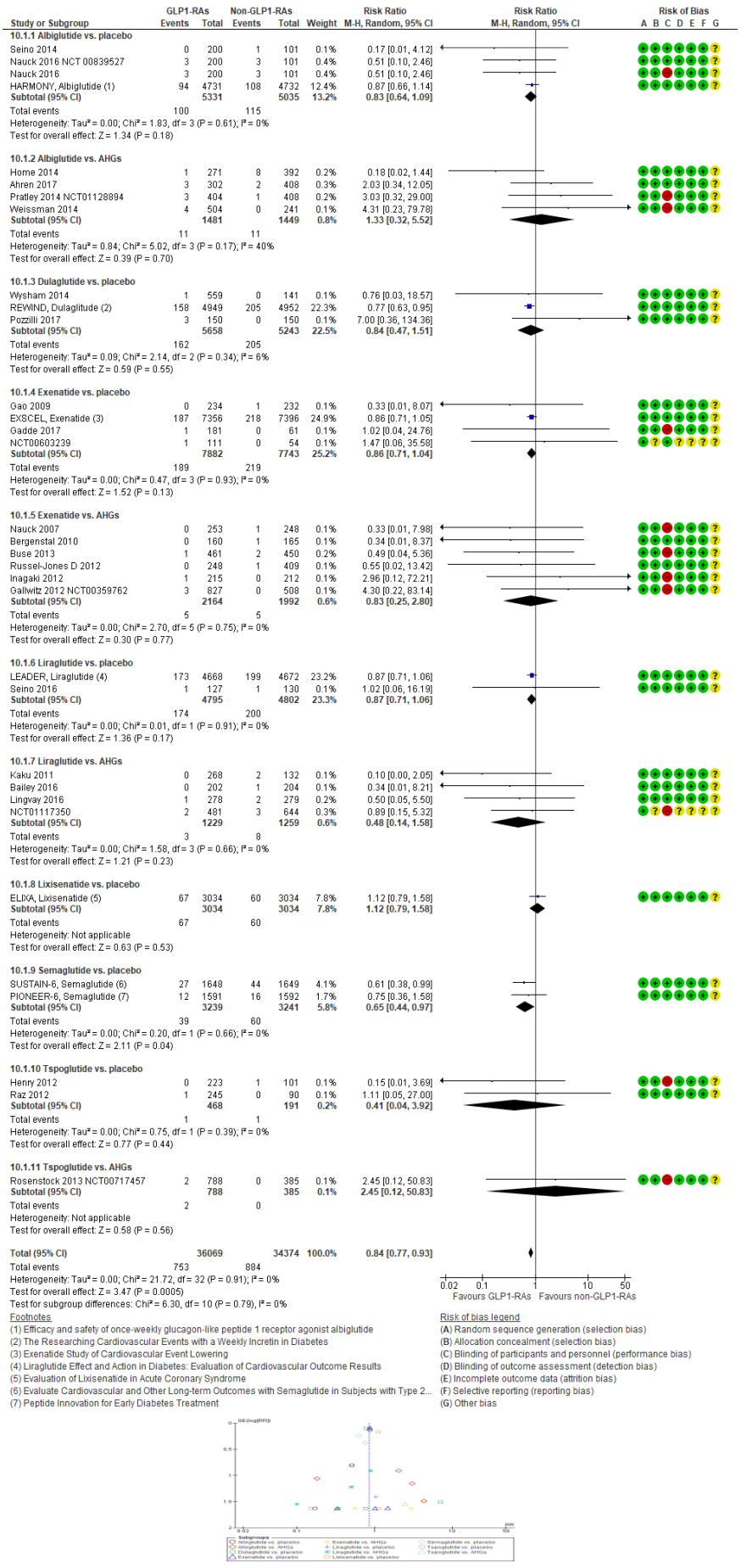

Figure 3-22. Forest and funnel plot of GLP1-RAs and stroke by GLP1-RAs treatment allocation sub-class, Random-effect model.

3.5.3 SGLT-Is Class

The overall rate of stroke was 1% in trials where SGLT2-Is were compared to non-SGLT-Is comparators. In 46 trials (52,949 participants; 846 stroke), the incidence of stroke with SGLT2-Is did not change from that versus placebo or active comparators of T2DM drugs (RR 1.01; 95% CI 0.89−1.16; *P*=0.84) using fixed-effect model. No differences were noted in the pooled data from random-effect model. There was no significant evidence of reporting bias or statistical heterogeneity across trials (I^2=0%). A summary table detailed the effects of the SGLT2-Is class and sub-class on stroke risk (Table 3-3).

Outcome or Subgroup	Studies	Participants	Effect Estimate Mantel-Haenszel, Fixed-effect test Risk Ratio (95% confidence intervals)
11.1 Risk of stroke by subtypes and treatment allocation (SGLT2-Is vs. non-SGLT2-Is)	**46**	**59869**	**1.01 [0.88, 1.15]**
11.1.1 Ischaemic stroke (SGLT2-Is vs. placebo)	33	42332	1.03 [0.89, 1.19]
11.1.2 Haemorrhagic stroke (SGLT2-Is vs. placebo)	4	1801	0.39 [0.10, 1.58]
11.1.3 Ischaemic stroke (SGLT2-Is vs. AHGs)	14	12067	0.94 [0.58, 1.52]
11.1.4 Haemorrhagic stroke (SGLT2-Is vs. AHGs)	3	3669	0.42 [0.08, 2.12]
12.1 Ischaemic stroke (SGLT2-Is vs. placebo)	**3**	**8538**	**0.74 [0.34, 1.61]**
13.1 Risk of stroke in T2DM by baseline characteristics (SGLT2-Is vs. non-SGLAT2-Is)	**46**	**52949**	**1.01 [0.89, 1.16]**
13.1.1 Risk of stroke in T2DM (SGLT2-Is vs. placebo)	23	11983	0.63 [0.38, 1.03]
13.1.2 Risk of stroke in T2DM (SGLT2-Is vs. AHGs)	14	12067	1.01 [0.64, 1.59]
13.1.3 Risk of stroke in T2DM and CVD (SGLT2-Is vs. placebo)	3	2349	0.70 [0.21, 2.32]
13.1.4 Risk of stroke in T2DM and CKD (SGLT2-Is vs. placebo)	6	26550	1.06 [0.92, 1.23]
14.1 Risk of stroke by clinical trial size (SGLT2-Is vs. non-SGLT2-Is)	**46**	**52949**	**1.01 [0.89, 1.16]**
14.1.1 SGLT2-Is vs. placebo (small RCTs)	30	16702	0.69 [0.46, 1.05]
14.1.2 SGLT2-Is vs. placebo (large RCTs)	2	24180	1.06 [0.92, 1.24]
14.1.3 SGLT2-Is vs. AHGs (small RCTs)	14	12067	1.01 [0.64, 1.59]
15.1 SGLT2-Is by treatment allocation sub-class	**46**	**52949**	**1.01 [0.88, 1.16]**
15.1.1 Canagliflozin vs. placebo	6	2693	0.82 [0.31, 2.19]
15.1.2 Canagliflozin vs. AHGs	5	5017	1.63 [0.65, 4.12]
15.1.3 Dapagliflozin vs. placebo	14	24172	0.97 [0.82, 1.15]
15.1.4 Dapagliflozin vs. AHGs	2	1348	1.13 [0.23, 5.62]
15.1.5 Empagliflozin vs. placebo	11	13555	1.13 [0.88, 1.47]
15.1.6 Empagliflozin vs. AHGs	6	5411	0.76 [0.43, 1.33]
15.1.7 Ertugliflozin vs. placebo	1	462	2.48 [0.12, 51.42]
15.1.8 Ertugliflozin vs. AHGs	1	291	0.17 [0.01, 4.07]

Table 3-3. A summary table detailed the effects of the SGLT2-Is class on the risk of stroke

3.5.3.1 SGLT2-Is and non-fatal stroke subtypes

The use of SGLT2-Is did not change the occurrence of stroke for either ischaemic (RR 1.03; 95% CI 0.89−1.19; *P*=0.68) or haemorrhagic (RR 0.39; 95% CI 0.10−1.58; *P*=0.19) events versus placebo. The use of SGLT2-Is did not decrease the occurrence of stroke for either ischaemic (RR 0.94; 95% CI 0.58−1.52; *P*=0.79) or haemorrhagic (RR 0.42; 95% CI 0.08−2.12; *P*=0.29) events versus active comparators of T2DM drugs. (Fixed-effect (Figure 3-23) and random-effect (Figure 3-24) model). The GRADE score was moderate (Supplemental Table 3-22).

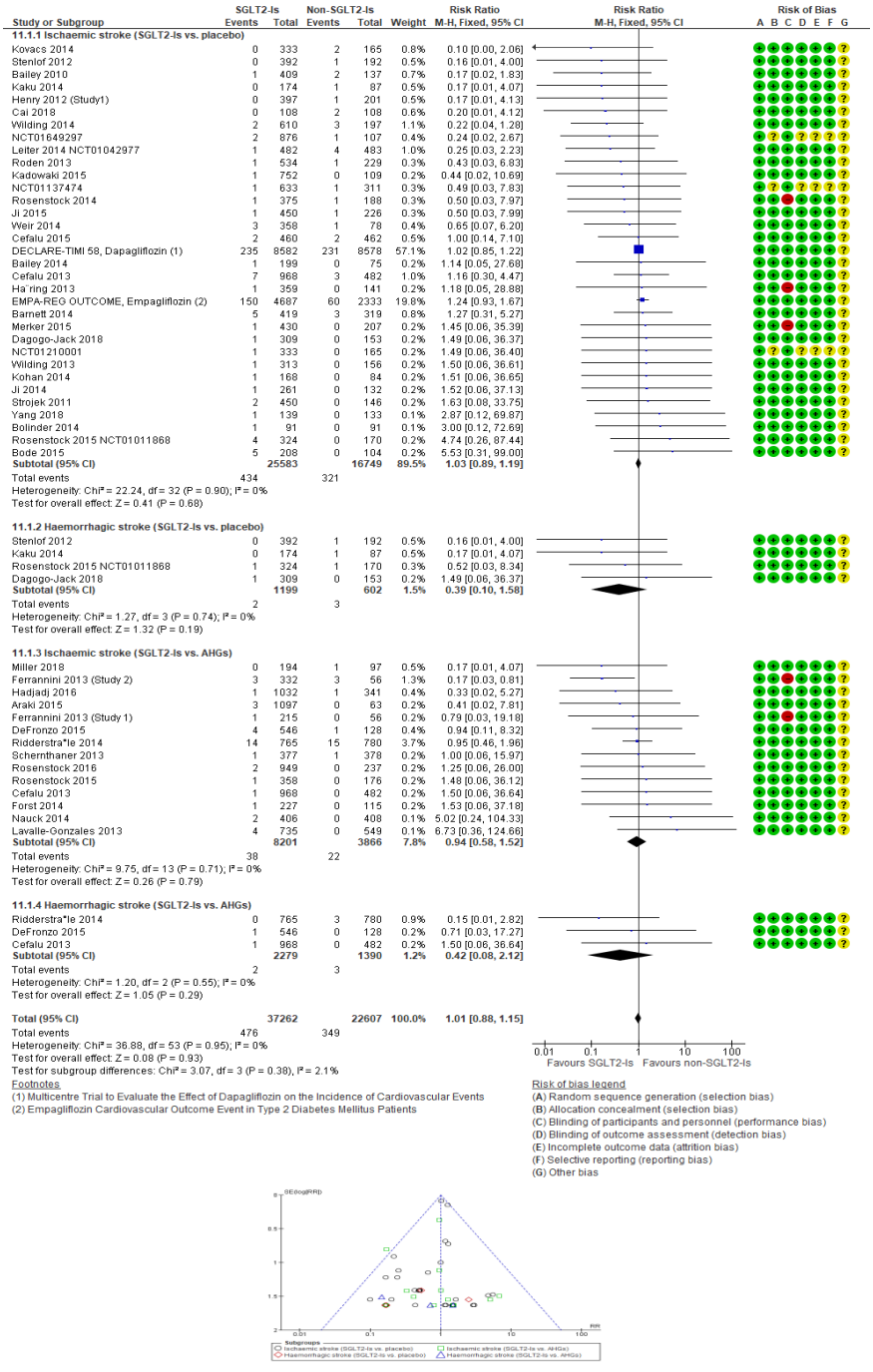

Figure 3-23. Forest and funnel plot of non-fatal stroke by subtypes with SGLTS-Is therapies, Fixed-effect model.

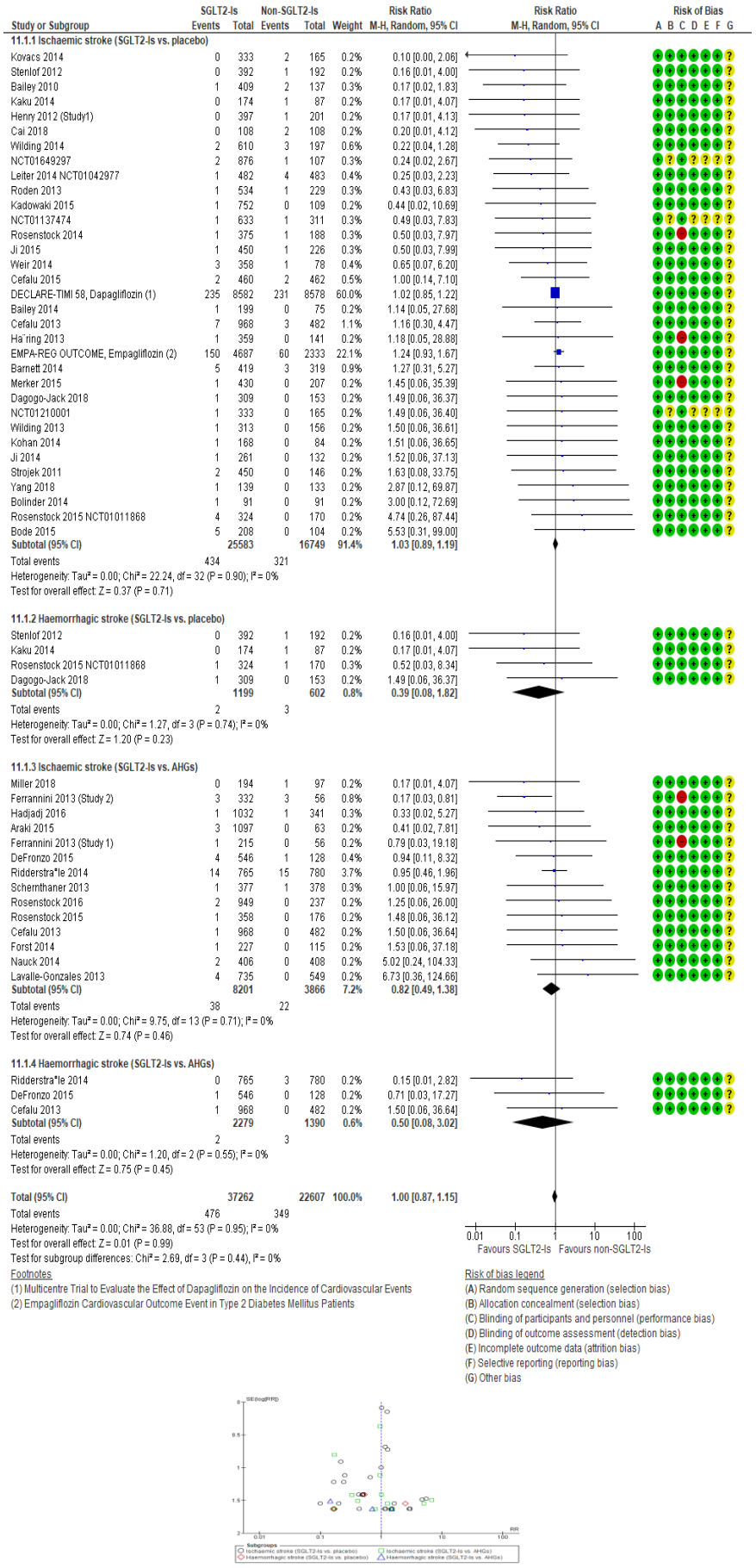

Figure 3-24. Forest and funnel plot of non-fatal stroke by subtypes with SGLTS-Is therapies, Random-effect model.

3.5.3.2 SGLT2-Is and fatal stroke risk

In three trials (8,538 participants with 25 stroke events), SGLT2-Is did not decrease the risk of fatal stroke (RR 0.74; 95% CI 0.34−1.61; *P*=0.45) versus placebo using fixed-effect (Figure 3-25) and random-effect (Figure 3-26) model. The GRADE score was low (Supplemental Table 3-23).

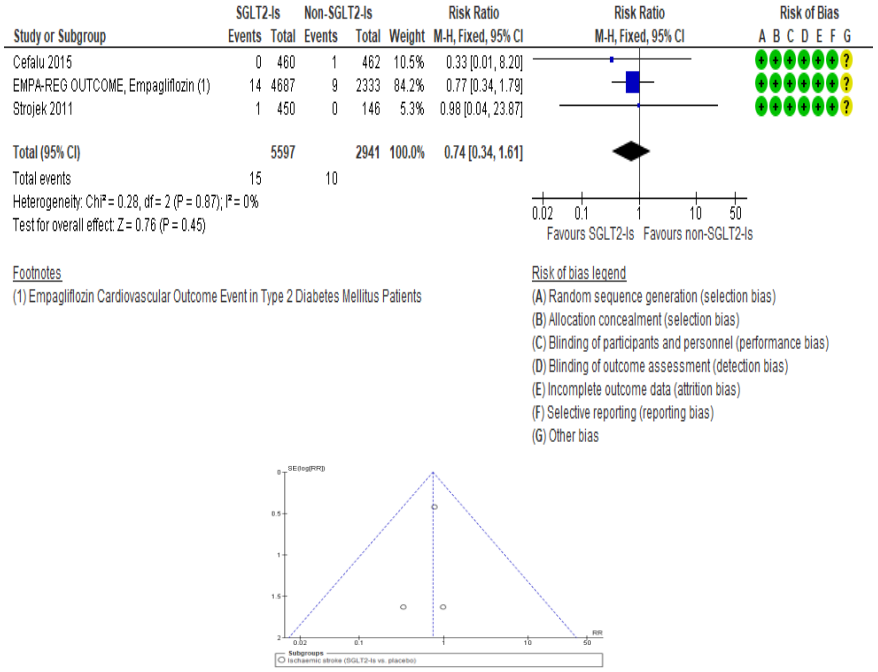

Figure 3-25. Forest and funnel plot of fatal stroke with SGLT2-Is therapies, Fixed-effect model.

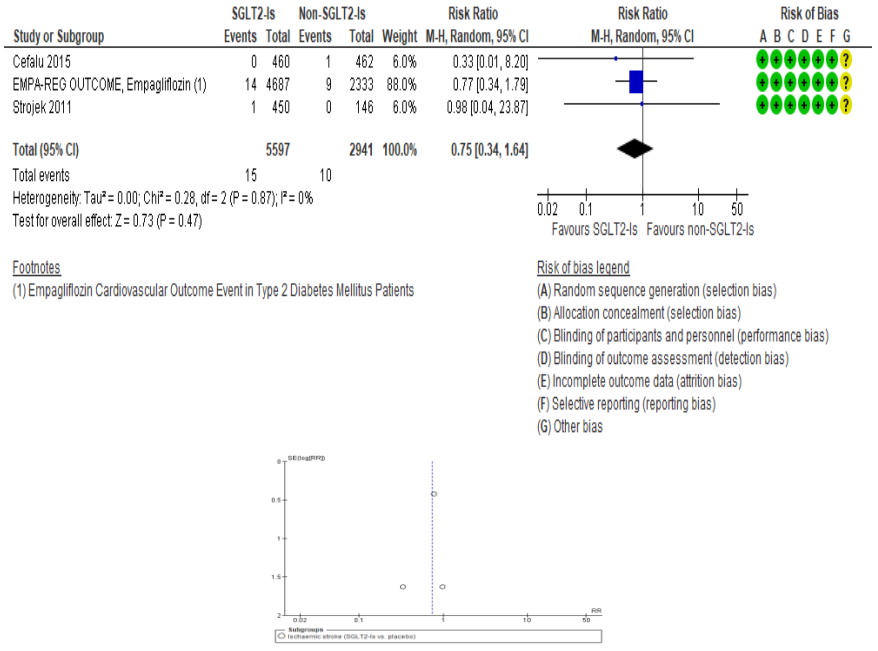

Figure 3-26. Forest and funnel plot of fatal stroke with SGLT2-Is therapies, Random-effect model.

3.5.3.3 SGLT2-Is by baseline characteristics

The use of SGLT2-Is did not change stroke risk in people with T2DM at risk of CVD or CKD endpoints (RR 1.01; 95% CI 0.89−1.16; *P*=0.84) versus non-SGLT2-Is using fixed-effect (Figure 3-27) and random-effect (Figure 3-28) model. The GRADE score was moderate (Supplemental Table 3-24).

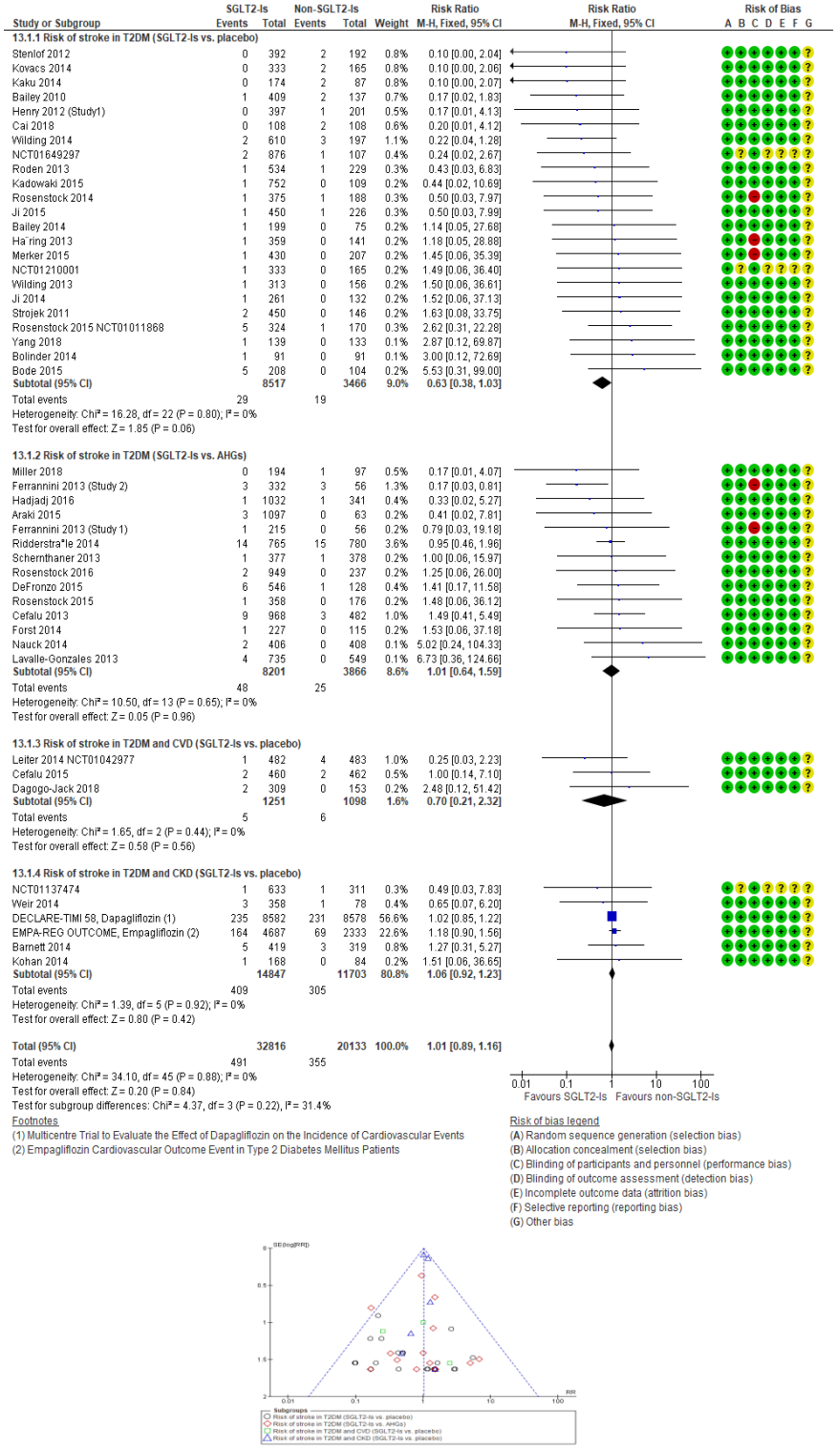

Figure 3-27. Forest and funnel plot of stroke by studies baseline characteristics with SGLT2-Is therapies, Fixed-effect model.

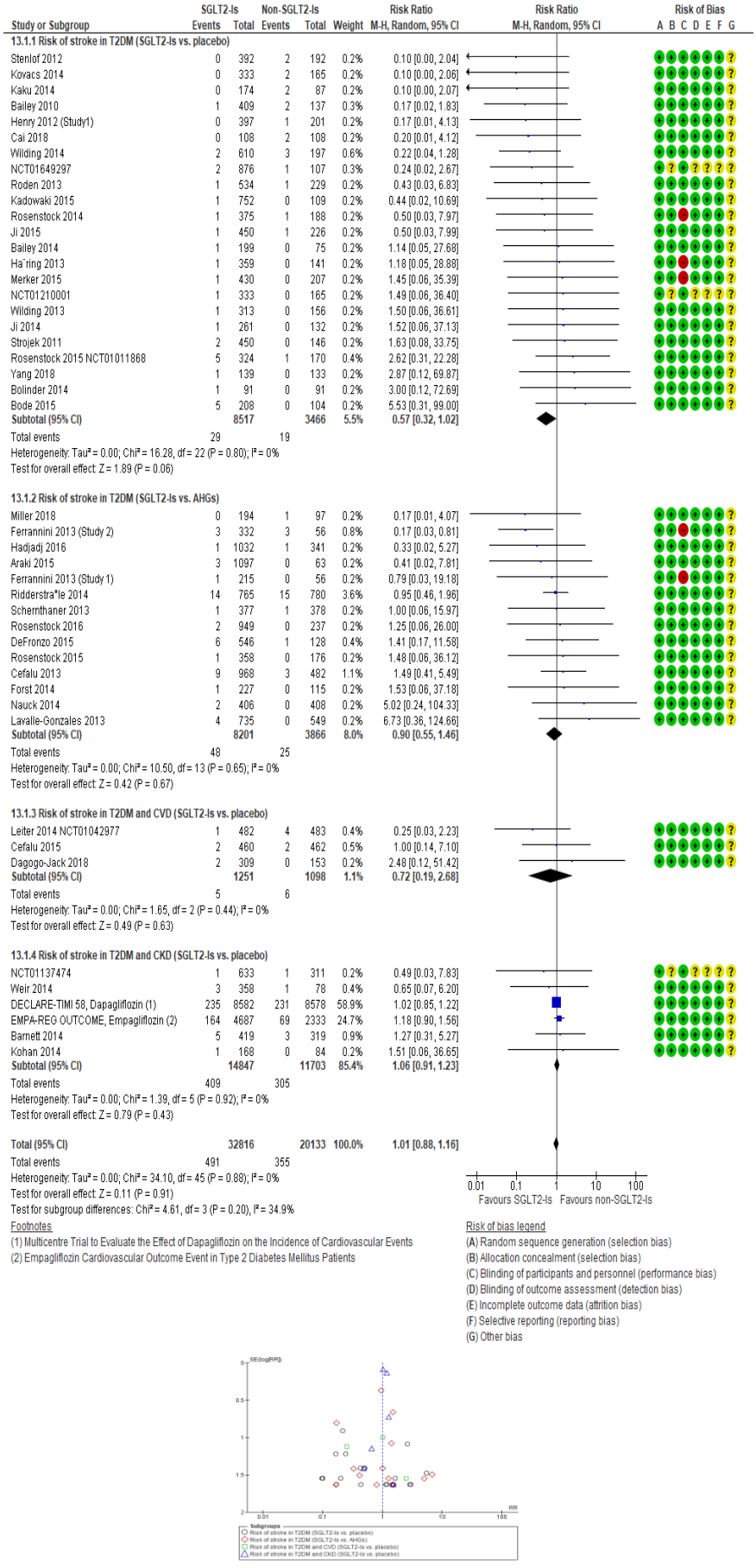

Figure 3-28. Forest and funnel plot of stroke by studies baseline characteristics with SGLT2-Is therapies, Random-effect model.

3.5.3.4 SGLT2-Is by clinical trial size

The use of SGLT2-Is did not decrease stroke risk from the pooled analysis of the large RCTs (RR 1.06; 95% CI 0.92−1.24; *P*=0.42) or small RCTs (RR 0.69; 95% CI 0.46−1.05; *P*=0.08) versus placebo or in small RCTs (RR 1.01; 95% CI 0.64−1.59; *P*=0.96) versus active comparators of T2DM drugs using fixed-effect (Figure 3-29) and random-effect (Figure 3-30) model. The GRADE score was moderate (Supplemental Table 3-25).

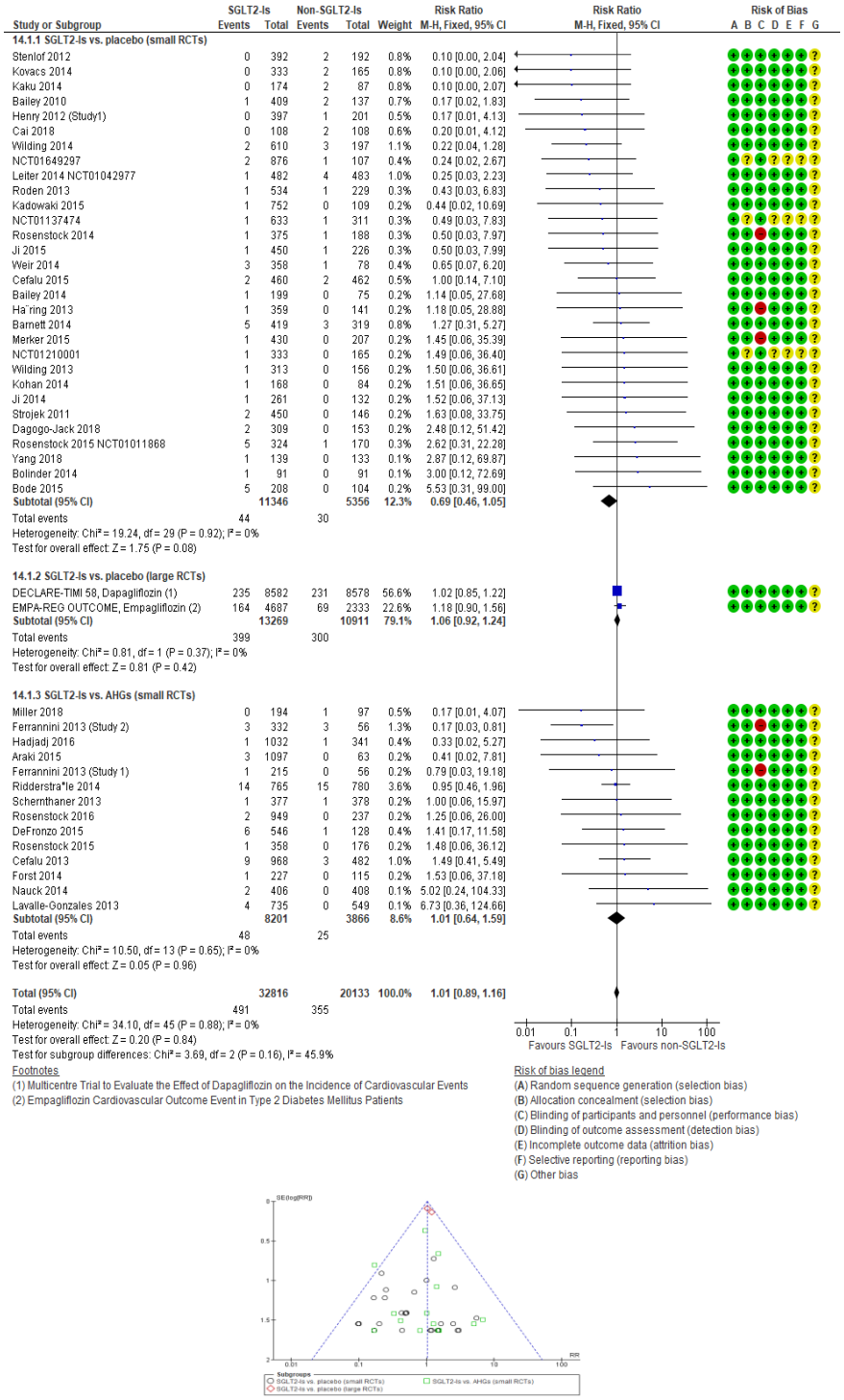

Figure 3-29. Forest and funnel plot of stroke by clinical trial size with SGLT2-Is therapies, Fixed-effect model.

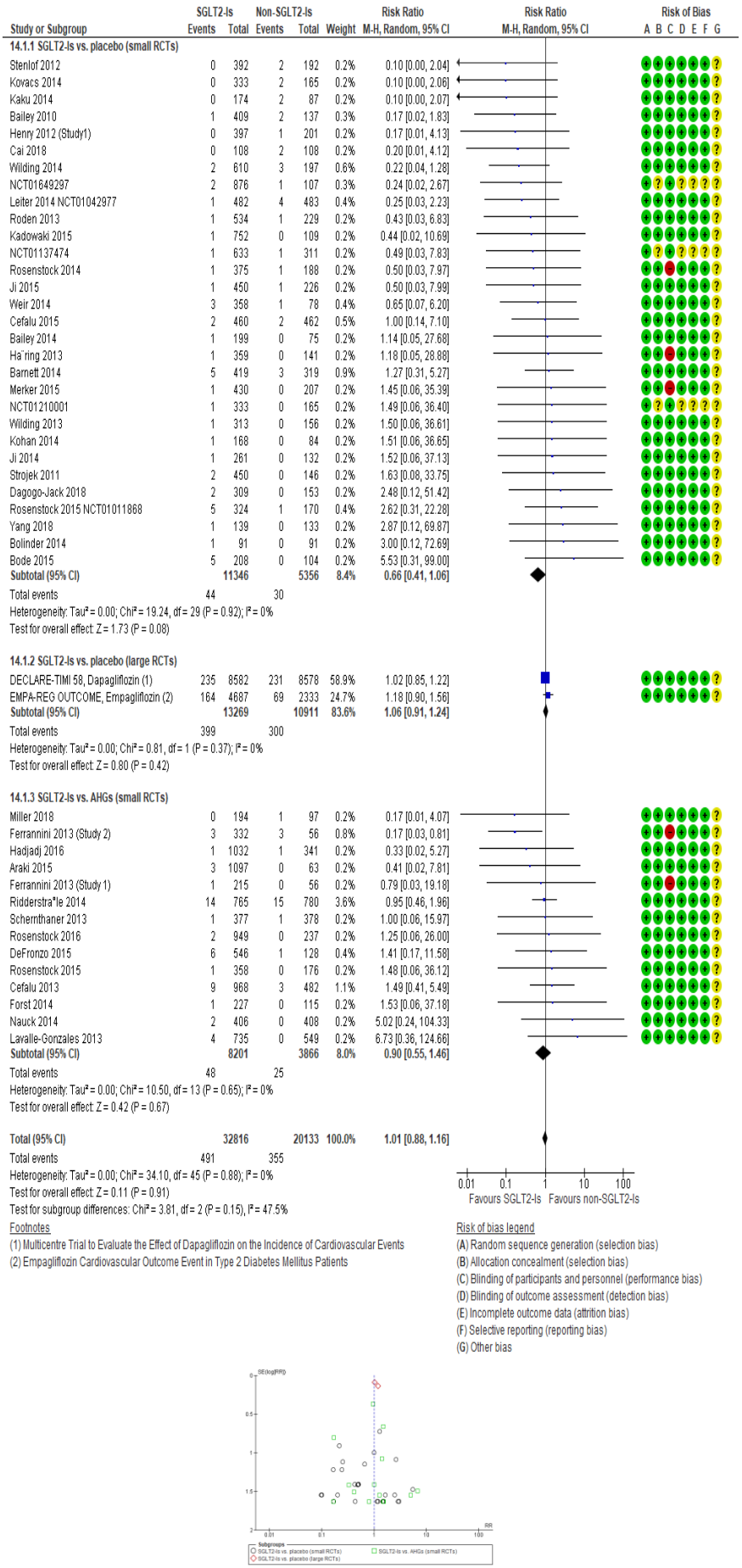

Figure 3-30. Forest and funnel plot of stroke by clinical trial size with SGLT2-Is therapies, Random-effect model.

3.5.3.5 SGLT2-Is and stroke by the type of SGLT2-Is treatment allocation sub-class stratification

The use of SGLT2-Is sub-class (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and ipragliflozin) did not decrease stroke risk (RR 1.01; 95% CI 0.88−1.16; *P*=0.89) versus placebo or active comparators of T2DM drugs. (Fixed-effect (Figure 3-31) and random-effect (Figure 3-32) model). The GRADE score was moderate (Supplemental Table 3-26).

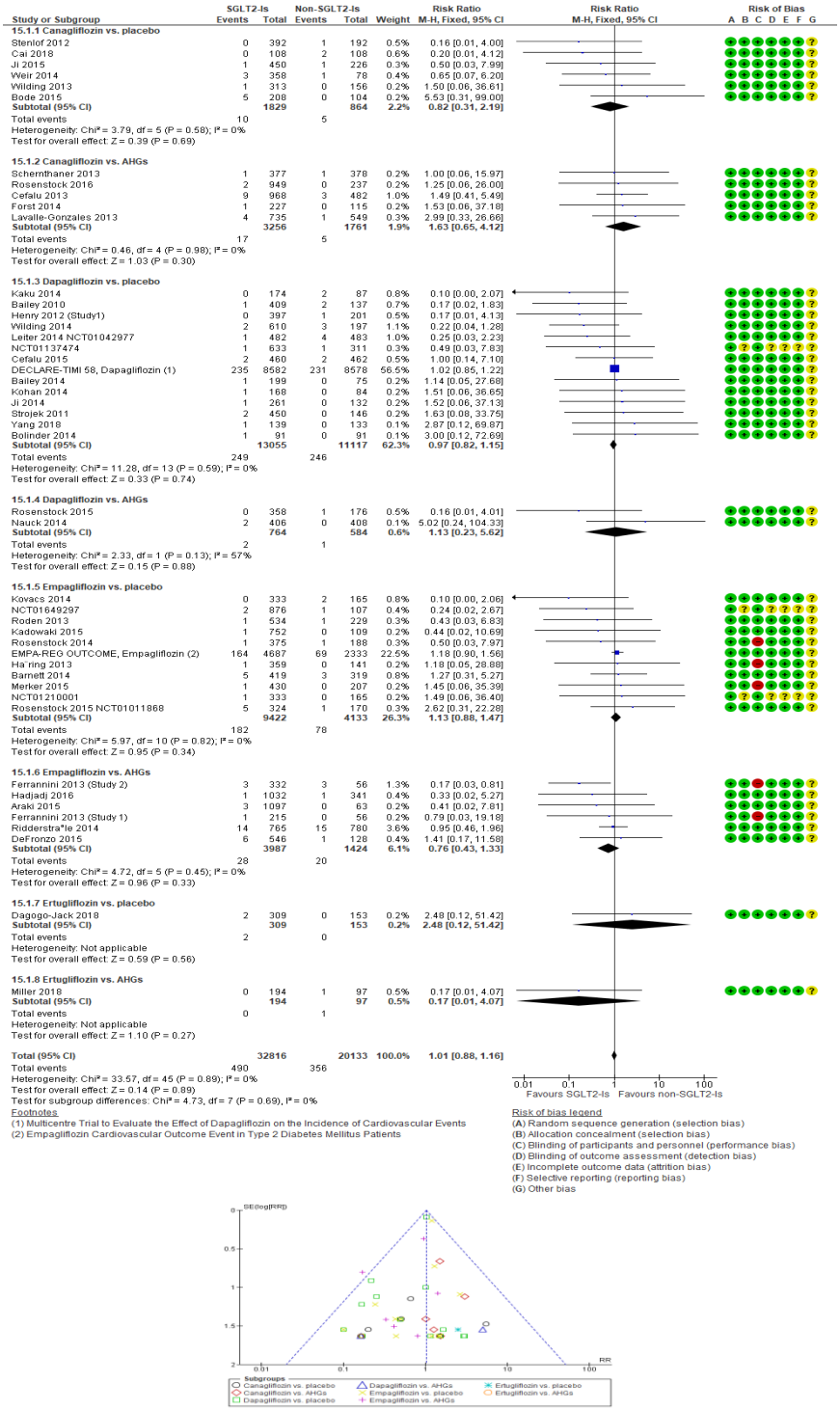

Figure 3-31. Forest and funnel plot of SGLT2-Is and stroke by SGLT2-Is treatment allocation sub-class, Fixed-effect model.

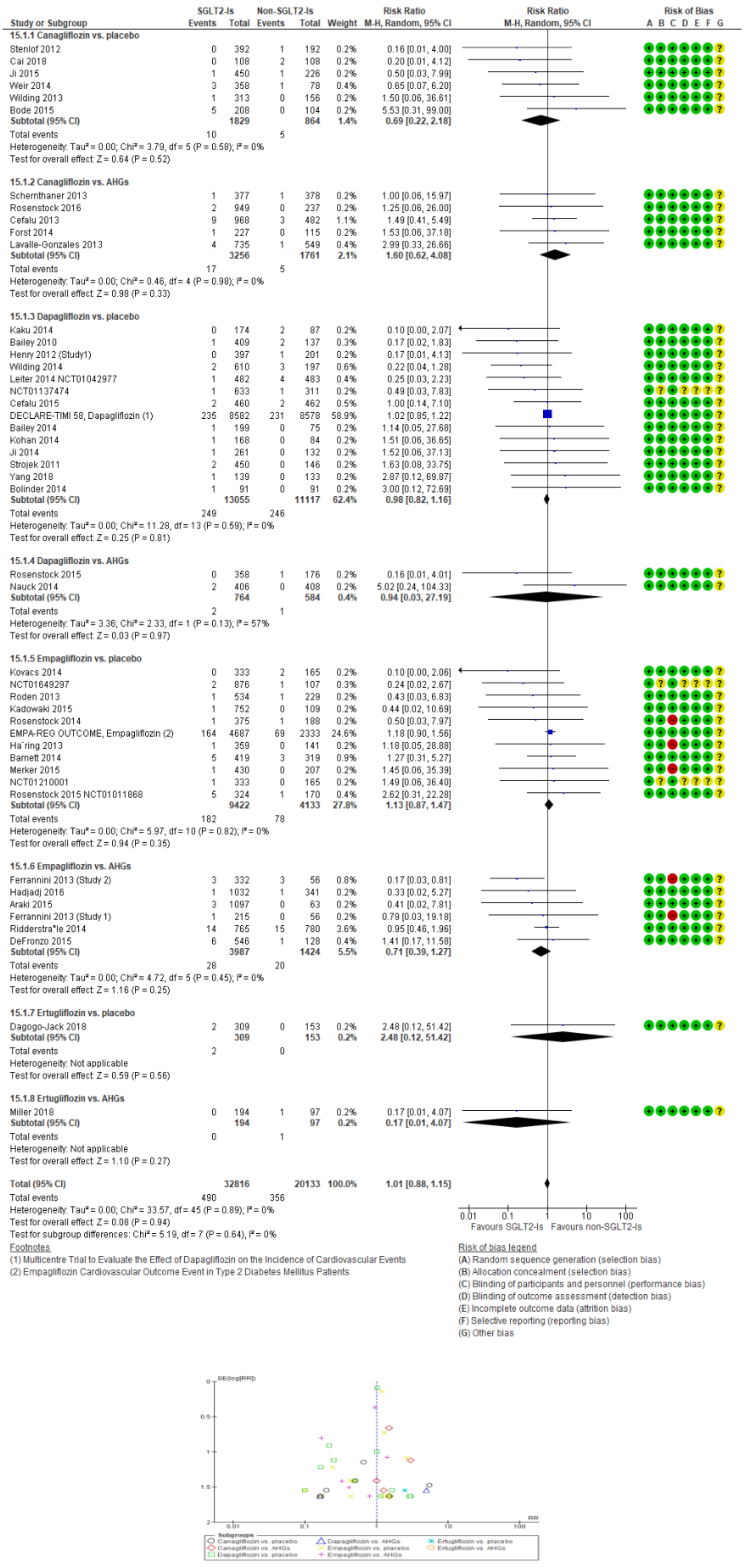

Figure 3-32. Forest and funnel plot of SGLT2-Is and stroke by SGLT2-Is treatment allocation sub-class, Random-effect model.

3.6 Discussion

The uncertainty of the effects of antidiabetic therapies on the risk of stroke has raised the question of the cerebrovascular safety of using these therapies for people with diabetes. We conducted a detailed review and meta-analysis to better understand stroke risk with the emerging antidiabetic therapies. We further found that adding new antidiabetic interventions to conventional treatment was associated with a variety of trends in stroke risk. In GLP1-RA drugs (but not DPP4-I or SGLT2-I drugs), stroke risk is decreased significantly in the T2DM population with >24 months of cumulative exposure versus placebo (AR 2.6%; ARD 0.4%) but not versus other active comparators for T2DM drugs.

We conducted our analyses specifically to predict the severity of stroke outcomes by subtype and the mortality risk related to stroke. Compared to DPP4-Is and SGLT2-Is, we found that GLP1-RAs had the strongest evidence for a reduction in the rate of ischaemic stroke versus placebo. However, such significant reduction dose not reflected to decrease the risk of fatal stroke versus placebo. The apparent discrepancy across drug classes raises a question as to whether such differences resulted due to the chance effect of these drugs on stroke risk. The observed trend towards less severe strokes with GLP1-RAs could be explained by the fact that DPP4-Is, unlike GLP1-RAs, do not cross the blood brain barrier and the GLP1 receptor is expressed in a wide range of tissues, including the heart, [402] brain and pancreas. [378] However, the observed (nonsignificant) effect of increased numeric stroke events with SGLT2-Is was derived mainly from the drug empagliflozin in the large Empagliflozin Cardiovascular Outcome Event in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome) trial. [398] It has been suggested that SGLT2-Is minimize brain infarct size by increasing the ketone levels and thus stimulating the neuroprotective effects of macrophages that reduce oxidative stress. [403] [404] However, the authors of the EMPA-REG Outcome trial pointed out an increase in haematocrit levels and therefore blood viscosity that they attributed as driving from a natriuretic effect, which raised the osmotic diuresis and subsequent dehydration. This might explain the nonsignificant stroke paradox [405] with SGLT2-Is.

Patients with diverse characteristics might yield diverse treatment effects. To limit the clinical heterogeneity across studies, we attempted to stratify stroke risk in people with T2DM by the baseline characteristics for a high risk of MACEs. We found that GLP1-RAs, (but not DPP4-I or SGLT2-I drugs), appear to decrease the risk of non-fatal stroke versus placebo in people with T2DM who are at high risk of CVD and/or CKD without significantly

decreasing the rate of non-fatal stroke in those with T2DM without CVD- or CKD-related risk. These patients represent a growing target population for controlling glycaemia to prevent micro- and macro-vascular disease progression. Whether these beneficial impacts relate to the direct effects of such drugs subclasses on stroke incidence or would translate differently or similarly if they were initiated earlier in the acute stroke population remains uncertain, as 5% of the total population in DPP4-Is and SGLT2-Is and 1.4% in GLP1-RAs class had documented previous stroke events within the included large RCTs in this review. Therefore, the observed stroke risk direction of minimum and maximum magnitude as a plausible explanation for these therapies may allow us to focus on their indirect cardio- or neuro-vascular prevention independently of glycaemic effects.

To avoid underestimating the results, [406] we attempted to predict stroke risk based on the size of the clinical trial. Although people with T2DM have a significant reduction in stroke risk with GLP1-RAs, this perceived benefit is mainly due to the large RCTs versus placebo. Individual subclasses of the GLP1-RAs family in these trials, however, yielded nonsignificant or neutral incidences of stroke events, with the exception of semaglutide [401] and dulaglutide [400] in the results of large studies. Although the pharmacodynamics profile is very similar across the drug class, the main differences among individual agents are seen in the pharmacokinetic properties and longer effect of semaglutide and dulaglutide (once-weekly that acts primarily on fasting glucose with a carryover effect on postprandial glucose with a peak plasma concentration post-injection of 48 hours with 4.5 days of elimination) compared to the short-acting effect of lixisenatide (once-daily that acts mainly on postprandial glucose with a peak plasma concentration post-injection of one to 3.5 hours with three hours of elimination). [407] [408] The pooled data from Phase IV, post-marketing trials revealed that DPP4-I and SGLT2-I therapies does not decrease stroke risk significantly versus placebo, which is in line with the results for Phase II and III studies versus placebo or controls. This finding is also in line with preclinical studies of ischaemic stroke. [378] However, we observe significant evidence of stroke reduction with the DPP4-Is (dutogliptin) class versus placebo in the Phase II and III studies. Thus, when interpreting these data, such subgroup analyses should be taken into consideration. Although our sample size was large, the number of stroke events in our meta-analyses of small trials was relatively low and thus the analysis may not have the statistical power to detect the small clinical differences in stroke event rates across groups. We based our conclusions on data from the fixed-effect method as significant heterogeneity was not detected across groups.

We attempt to predict stroke risk with DPP4-Is, GLP1-RAs and SGLT2-Is agents versus active comparators of T2DM drugs individually. No evidence of stroke reduction was seen with these individual new antidiabetic classes versus active comparators of T2DM drugs. The meta-analyses of individual active comparators of T2DM treatments are reported in (Supplemental Figure 3-2 and Supplemental Figure 3-3 for DPP4-Is, Supplemental Figure 3-4 and Supplemental Figure 3-5 for GLP1-RAs and Supplemental Figure 3-6 and Supplemental Figure 3-7 for SGLT2-Is). We did observe significant evidence of stroke reduction with DPP4-Is class versus sulfonylurea, but this association was only evident in the fixed-effect model. It is important to acknowledge that the largest postmarketing trial in this analysis is the Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA), [388] which did not prove a clinically relevant stroke reduction with DPP4-Is use versus glimepiride. This meta-analysis, which pooled Phase II and III premarketing trials, was therefore relatively insensitive for cardiovascular risk assessment, which makes it necessary to conduct dedicated Phase IV postmarketing cardiovascular outcome trials to substantiate any risk signals. Therefore, such heterogeneity in trial design that arise across groups may influence the overall effect estimate of stroke reduction with DPP4-Is class versus sulfonylurea.

The chemotherapeutic advances in diabetes management have increased the difficulty of demonstrating the favourable neuro-preventive impacts of their intensified use. Strides have been made in addressing their beneficial effects on stroke risk, although more and longer follow-ups are required than what routinely occur in clinical trials. [409] Still, the evidence remains uncertain as to whether metformin [74] decrease CVD mortality rates, or if the rates increase with sulfonylureas. [410] In the present meta-analysis comparing the DDP4-I and SGLT2-I classes, the stroke data from clinical trials suggested that the administration of GLP1-RAs for five years in 100 people with T2DM at risk of MACEs is expected to decrease the stroke risk in three patients (1 fewer to 0 fewer) versus placebo. Previous pooled analyses of DPP4-I, [411] [412] SGLT2-I [411] [413] [414] and GLP1-RAs [415] therapies yielded discordant results, with either unchanged, decreased or increased in the incidences of cardiovascular events, MACEs and stroke. These large-scale trials were focused on companied MACEs outcomes. However, unlike the PROactive and IRIS trials, [377] which demonstrated a neuro-preventive putative effect of pioglitazone use in diabetic and nondiabetics individual with the antecedents of stroke/TIAs. No such analyses in people with stroke were available for studies with these new diabetic therapies.

This review represents the first study intended to evaluate the non-fatal and fatal ischaemic and haemorrhagic stroke impacts for DDP4-I, GLP1-RA and SGLT2-I use independently versus placebo or other antidiabetic classes and sub-classes based on recently published large RCTs. [388] [389] [392] [396] [397] [400] We also stratified our analysis to predict the risk of stroke in large versus small clinical studies across T2DM populations at risk or not at risk for CVD or CKD endpoints in order to determine their magnitude impacts on stroke outcomes. Although some non-cardiovascular trials with metabolic endpoints reported stroke risk as a single event, combining their findings with those of large trials that reported stroke risk from MACEs endpoints as subgroup analyses of one greater meta-analysis. We relied on such stroke endpoints in this meta-analysis, thus providing a robust analysis of stroke outcomes for these new classes of antidiabetic therapies.

There are various caveats to this evidence that need to be acknowledged. In this review, the reliability of the included trials was based on stroke data in people with diabetes at a high risk of stroke, which may therefore affect the generalisability of these findings in people with the antecedents of stroke. Although the majority of large trials were conducted with relatively long follow-up periods, the non-fatal and/or fatal stroke outcomes were taken from the primary or secondary MACEs endpoints as censoring events or as an exposure time to the first stroke. We could not predict the risk of recurrent strokes with these therapies. Consequently, none of these studies predicted or stratified recurrent events in people with strokes according to aetiological stroke types or subtypes or by the severity impact of stroke across gender differences. In this regard, the target diabetic patients appeared to show diverse interventional responses with these new antidiabetic therapies.

3.7 Conclusion

The GLP1-RAs may reduce non-fatal stroke risk versus placebo, but there was no evidence of a reduction in stroke rate with DPP4-I or SGLT2-I agents. These findings may help stroke physicians guide the treatment of T2DM in people at low or high risk of MACEs or stroke.

Chapter 4 Pioglitazone Use After Stroke. Exploring Stroke Survivors' Views – The PIOSurvey

4.1 Introduction

Stroke is common in the United Kingdom (UK) and is attended by the risk of recurrence. This risk is especially high during the first three months following stroke. [15] The European [265] and American [250] stroke and transient ischaemic attacks (TIAs) guidelines recommend the use of appropriate anti-thrombotic therapy, blood-pressure reduction and lipid-lowering treatments to reduce the risk of recurrent ischaemic strokes.

New treatments are needed to reduce the risk of stroke and recurrence. Pioglitazone, [92] a drug from the thiazolidinedione family, may prevent strokes and heart attacks after stroke in people who are resistant to insulin (hazard ratio (HR) 0.76 95% CI 0.62−0.93; P=0.007) in the Insulin Resistance Intervention after Stroke (IRIS) trial. [93] The absolute risk reduction was 3%. This reduction is comparable to the changes seen with aspirin [97] and statins. [98] [99] Interestingly, about half as many (HR 0.48; 95% CI 0.33−0.69; P<0.001) of the IRIS patients treated with pioglitazone went on to develop diabetes. Given the high early recurrence rate after strokes despite advances in stroke treatments, the use of pioglitazone as early as possible post-stroke is worthy of consideration due to its effectiveness in stroke recurrence prevention without an increased risk of bleeding or haemorrhagic transformation (HR 1.00; 95% CI 0.50–2.00; P=1.00). [416] However, the net benefit of this drug has been questioned as it associated with increased risks for fractures, [141] by a smaller but not insignificant amount, weight gain and/or peripheral oedema. [198] Balancing such possible benefits and risks in the favour of people with strokes is an uncertain and challenging task.

We have surveyed UK stroke physicians and found that pioglitazone is not used. [417] Pioglitazone is a drug already used to treat type 2 diabetes so is widely available and cheap. The stroke guidelines [293] stipulate that pioglitazone can be considered for use in individual patients after considering the risks and benefits. There is little data on the stroke survivor's perspective concerning the trade-offs between the benefits and potential side effects (SEs) of pioglitazone. It is possible, though, that the frequency of these SEs could be reduced by targeting interventions via better patient selection, dose reductions, the use of fracture-preventive therapies and lifestyle measures. We conducted a survey to explore the views of people with stroke on the post-stroke use of pioglitazone to help us decide whether further clinical trials of pioglitazone are needed and at best how to minimise the risks associated with pioglitazone use in the stroke population. Ultimately, gaining clarity in this

regard will help with the design of a clinical trial that meets the needs of and is acceptable to stroke survivors.

4.2 Methods

4.2.1 Study design

The study was performed according to the Research Governance Framework for Health and Community Care. It was approved by the West of Scotland Research Ethics Committee of the National Health Service (NHS). The study was piloted and reviewed, and the protocol was registered via the UK Integrated Research Application System, 238470. [418]

4.2.2 Study population

The participants were stroke survivors registered in the Scottish health research register SHARE. [419] SHARE is an NHS Research Scotland initiative created to establish a register of people interested in participating in health research and who agree to allow SHARE to access their NHS computer records to check whether they might be suitable for a research study. We used this platform to identify potentially eligible people, aged >18 years, who had suffered strokes or TIAs and to invite them to answer our survey. The online survey was created and hosted by Bristol On-line Surveys (BOS). An online format was used to maximise the response return and the ease of dissemination. The survey was distributed via email with a hyperlink embedded to allow access to www.onlinesurveys.ac.uk.

4.2.3 Identification of participants and consent

Potential participants received an invitation letter from SHARE detailing the project background, Supplemental Figure 4-1. The invitation included a participant information sheet, Supplemental Figure 4-2. All participants were asked to confirm that they had read the sheet and to consent to completing the questionnaire. A timeline was given to consecutive participants between March and May 2019. Responders were given 10 weeks to complete the survey, with a reminder to be sent two weeks prior to the closing date if we received less than 100 responses. All questionnaires were anonymous, and no personal data were collected.

4.2.4 The survey

The study involved a structured survey. The validity of the survey content was assessed through a piloted draft, which was circulated to a small cohort of SHARE participants and amended based on their feedback to reduce the complexity of the questions. The survey was then sent to a wider group of SHARE participants after the authors reached consensus on the final version of the survey. The technical functionality of the electronic questionnaire was tested before its release.

The questions aimed to elicit the views of the stroke survivors concerning pioglitazone use after stroke. The survey consisted of 23 questions, Supplemental Figure 4-3. It begins by providing information concerning the benefits and risks of pioglitazone use. The first question confirmed that participants had suffered a stroke or TIA and instructed that the questionnaire should only be completed by the person to whom it was sent. The following seven questions explored the basic demographic details of responders. Then participants were asked to express their opinions, using the five-point Likert scale, regarding the benefits of pioglitazone use, their concerns with the associated SEs, the acceptability of attempts to minimise SEs, their willingness to take pioglitazone and whether they would be willing to take part in future clinical trials.

We followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [420] and good practices in the reporting and conducting of our survey research.

4.2.5 Statistical analyses

Descriptive statistics were produced to summarise the survey responses. For categorical variables, the responses to the multiple-choice questions and the "Yes/No" answer items were calculated with numbers (participant number (percentage (%)). All analysis was performed using the BOS statistical software. Missing responses were minimized by adjusting the questionnaire setting on the BOS that 'each question should be mandatory answered before proceeding to the next one by the participants'.

4.3 Results

A total of 2,335 electronic invites were sent. Of these, 714 were read and 154 respondents completed the survey. The survey response rate was 28%. However, in nine of the completed questionnaires, the consent box giving permission to use the anonymous answers was not

checked. We therefore excluded these data and so we only analysed a total of 145 questionnaires. All responders were from Scotland.

4.3.1 Demographics data

The survey participants' ages were ≥30-80 years. Of the participants, 58 (40%) of them were aged ≥60-69 years, 111 (77%) had suffered strokes and 84 (58%) had suffered TIAs. Of the total participants, 97 (67%) of them were male. About half of the stroke survivors had hypertension (75 (52%)), diabetes mellitus (24 (17%)), ischaemic heart disease (angina or heart attack) (22 (16%)) or had experienced heart failure (5 (4%)). In addition, 9 (7%) had a history of bone fractures and 7 (5%) osteoporosis. A majority of the stroke survey patients had a family history of hypertension (68 (47%)) or ischaemic heart disease (48 (33%)). Most of the participants (122 (85%)) were taking lipid-lowering drugs. In addition, 101 (70%) were taking anti-platelets, 77 (54%) anti-hypertensives, 37 (26%) an anticoagulant and 22 (16%) glucose-lowering medications or vitamin D and calcium supplements. A minority of respondents (4 (3%)) were on osteoporotic drugs. The baseline characteristics of the stroke survivors included in the PIOSurvey is detailed in (Table 4-1).

Table 4-1. Baseline characteristics of the stroke survivors included in the PIOSurvey

Baseline characteristic of the stroke survivors	Participant number (percentage (%))
Age, year	
≥30- 39 years	3 (2.1%)
≥40- 49 years	7 (4.8%)
≥50- 59 years	23 (15.9%)
≥60- 69 years	58 (40%)
≥70- 79 years	36 (24.8%)
≥80 years	18 (12.4%)
Gender	
Female	48 (33.1%)
Male	97 (66.9%)
Prior stroke	
Yes	111 (76.6%)
No	34 (23.4%)
Prior TIAs	
Yes	84 (57.9%)
No	61 (42%)
Baseline health conditions	
Ischaemic heart disease (angina or previous heart attack)	22 (15.2%)
Heart failure	5 (3.4%)
High blood pressure (hypertension)	75 (51.7%)
Diabetes mellitus	24 (16.6%)
Bone fracture	9 (6.2%)
Osteoporosis	7 (4.8%)
Other (not specified)	51 (34.2%)
Health conditions in stroke survivor's family	
Ischaemic heart disease (angina or previous heart attack)	48 (33.1%)
Heart failure	25 (17.2%)
High blood pressure (hypertension)	68 (46.9%)
Diabetes mellitus	28 (19.3%)
Bone fracture	4 (2.8%)
Osteoporosis	8 (5.5%)
Other (not specified)	45 (31.0%)
Baseline medications	
Cholesterol lowering drugs (statins or fibrate)	122 (84.1%)
Antiplatelet blood thinners (aspirin or clopidogrel)	101 (69.7%)
Anticoagulant blood thinners (warfarin, dabigatran, apixaban, edoxaban or rivaroxaban)	37 (25.5%)
Blood pressure lowering drugs (angiotensin-converting enzyme inhibitors, beta-blockers, water tablets or calcium channel blockers)	77 (53.1%)
Drugs for diabetes (metformin, gliclazide, insulin or other injectable drugs)	22 (15.2%)
Drugs for osteoporosis (alendronate or risedronate)	4 (2.8%)
Vitamin D or calcium supplements	22 (15.2%)
Other (not specified)	4 (2.8%)

4.3.2 Views on pioglitazone therapy and side effects

The responses to the SEs related to pioglitazone therapy varied across participants. A total of 96 (66%) were unlikely/very unlikely to take pioglitazone and only 28 (20%) were likely/very likely to take it (Figure 4-1).

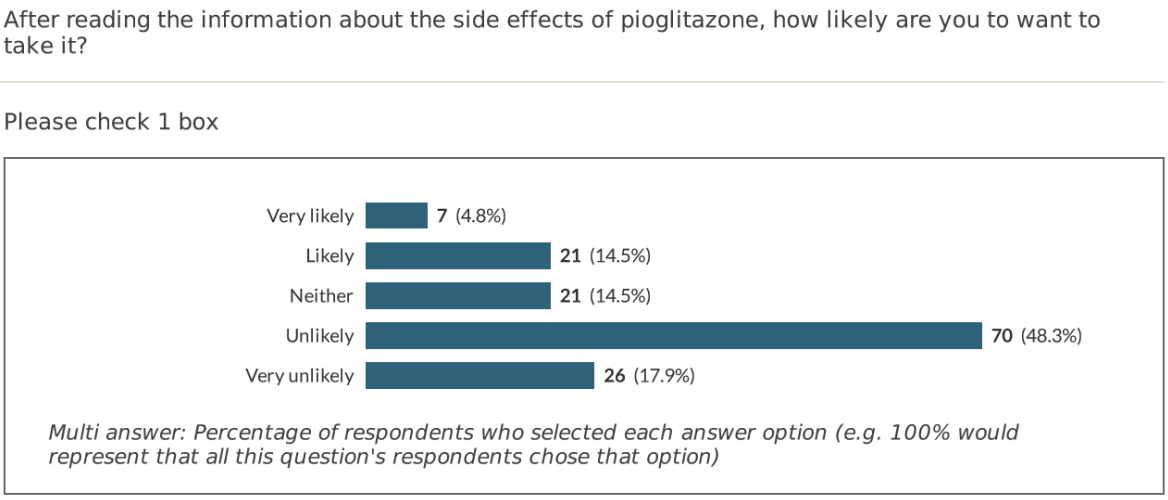

Figure 4-1. Stroke survivors' views to take pioglitazone therapy

A majority of the survey participants (124 (85%)) scored the weight gain SE with pioglitazone use as a significant main concern for them compared to ankle swelling or fracture SEs. Nearly, three-quarters of the responders (106 (73%)) rated ankle swelling as very important/important. Approximately two-thirds of participants (93 (65%)) rated fracture SEs as very important/important to them (Figure 4-2, Figure 4-3 and Figure 4-4).

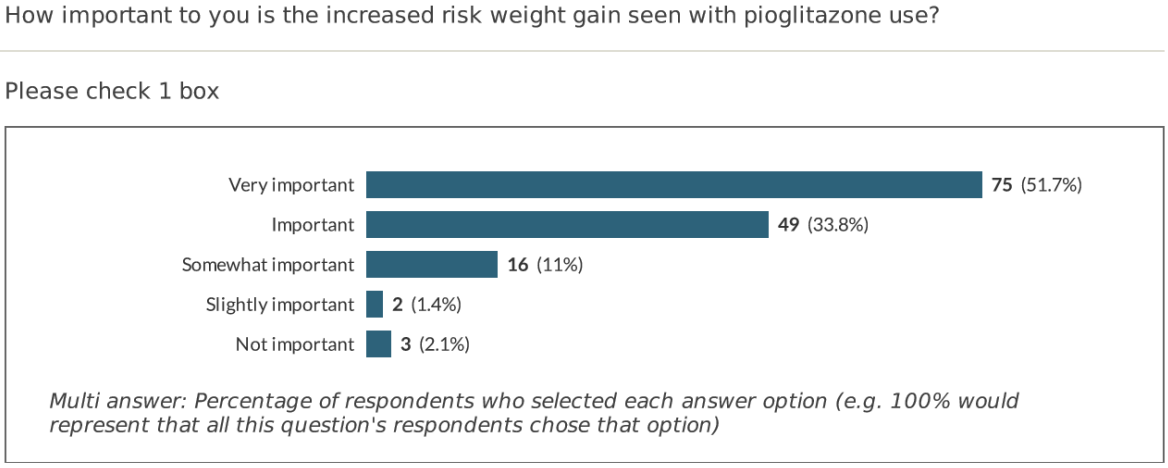

Figure 4-2. Stroke survivors' views on weight gain SEs associated with pioglitazone use

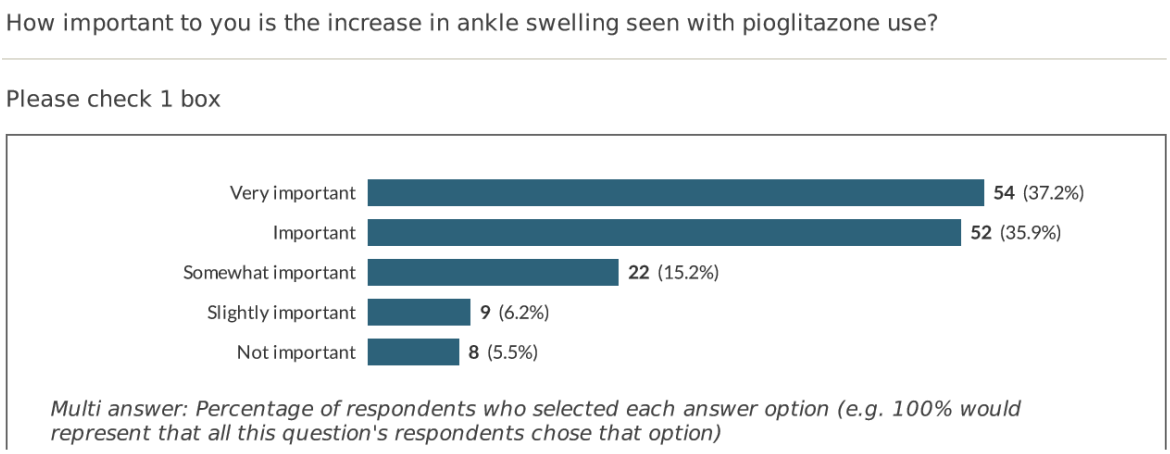

Figure 4-3. Stroke survivors' views on ankle swelling SEs associated with pioglitazone use

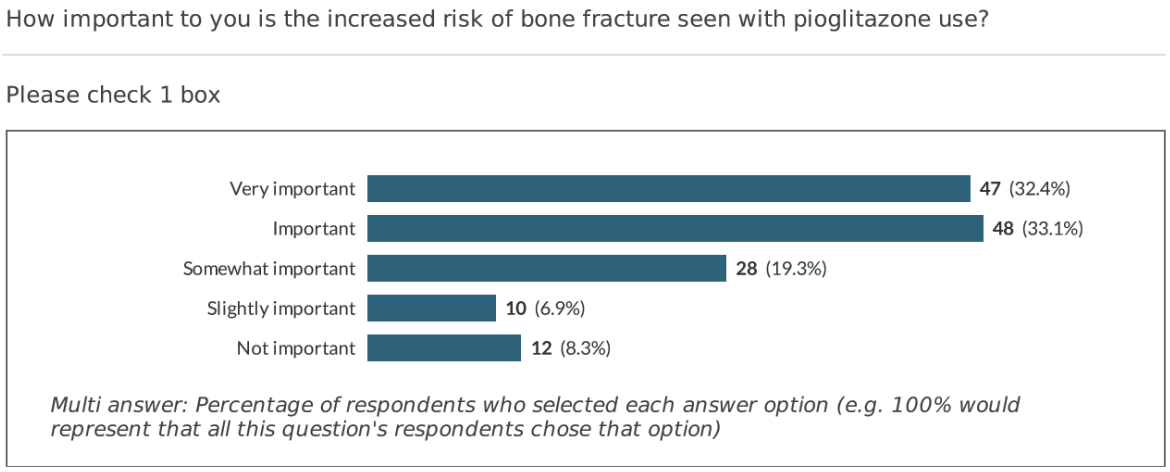

Figure 4-4. Stroke survivors' views on fractures SEs associated with pioglitazone use

However, compared to these SEs with pioglitazone use, 78 (53%) of participants rated avoiding stroke and MI recurrences or the development of diabetes as very important/important to them (Figure 4-5, Figure 4-6).

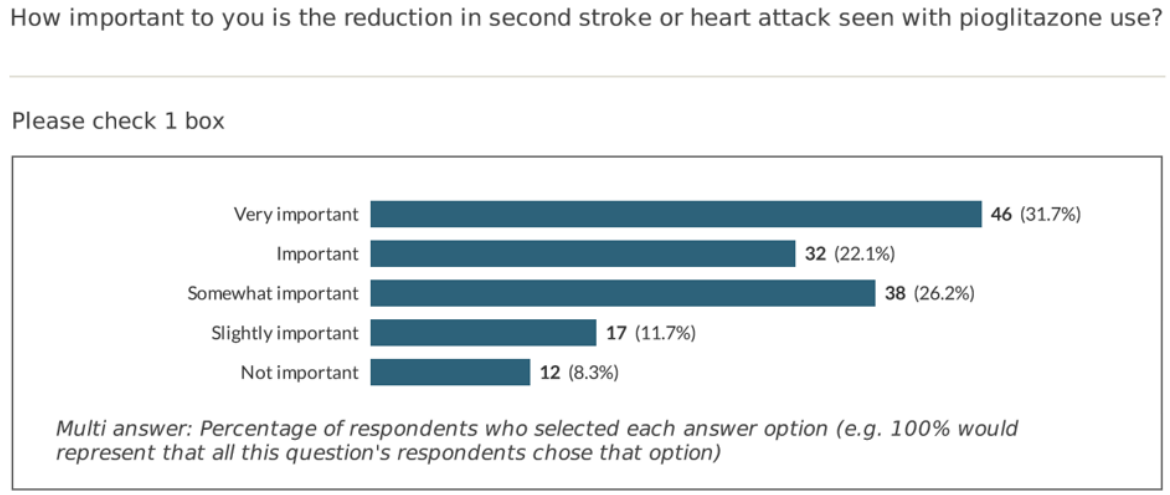

Figure 4-5. Stroke survivors' views on the reduction in second stroke or heart attack associated with pioglitazone use

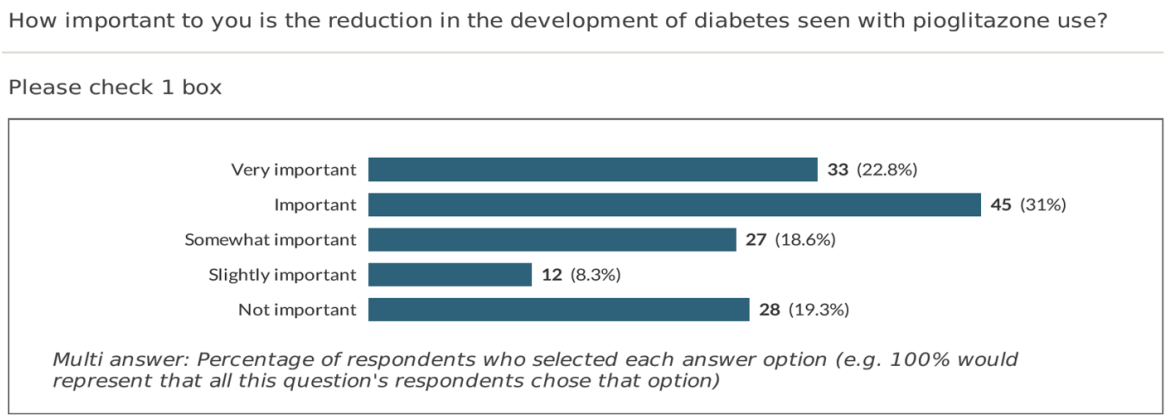

Figure 4-6. Stroke survivors' views on the development of diabetes with pioglitazone use

4.3.3 Acceptability of strategies to mitigate the side effects of pioglitazone therapy

A total of 65 respondents (45%) would be likely/very likely to take pioglitazone if there was no increased risk of weight gain. In comparison, 53 respondents (37%) were unlikely/very unlikely to take the drug due to the weight gain SE (Figure 4-7).

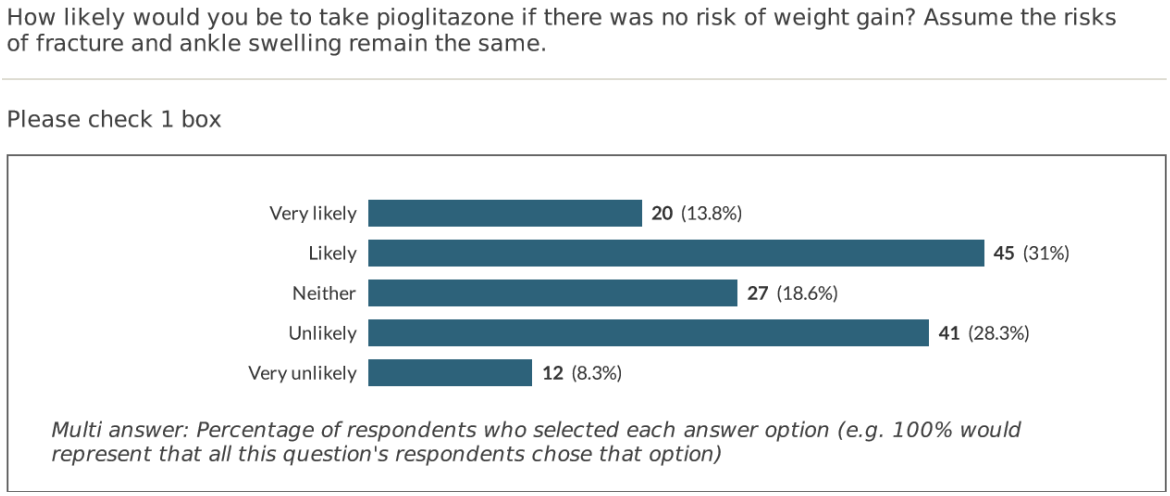

Figure 4-7. Stroke survivors' views on weight gain SEs associated with pioglitazone use

However, 103 respondents (72%) indicated they would be were likely/very likely to take pioglitazone if the SE weight gain were prevented with lifestyle measures of controlled diet and exercise compared to 29 (20%) who were still unlikely/very unlikely to take it (Figure 4-8).

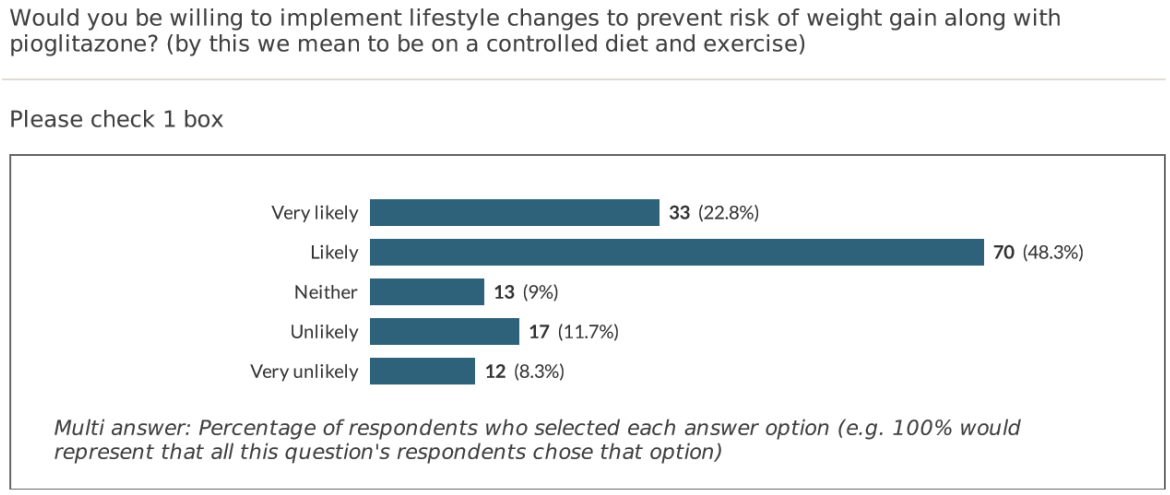

Figure 4-8. Stroke survivors' views on implementation of lifestyle for weight gain SEs associated with pioglitazone use

Fifty participants (35%) indicated they would be willing to take pioglitazone if there was no increased risk of ankle swelling compared to 61 (42%) who were still unlikely/very unlikely to take it (Figure 4-9).

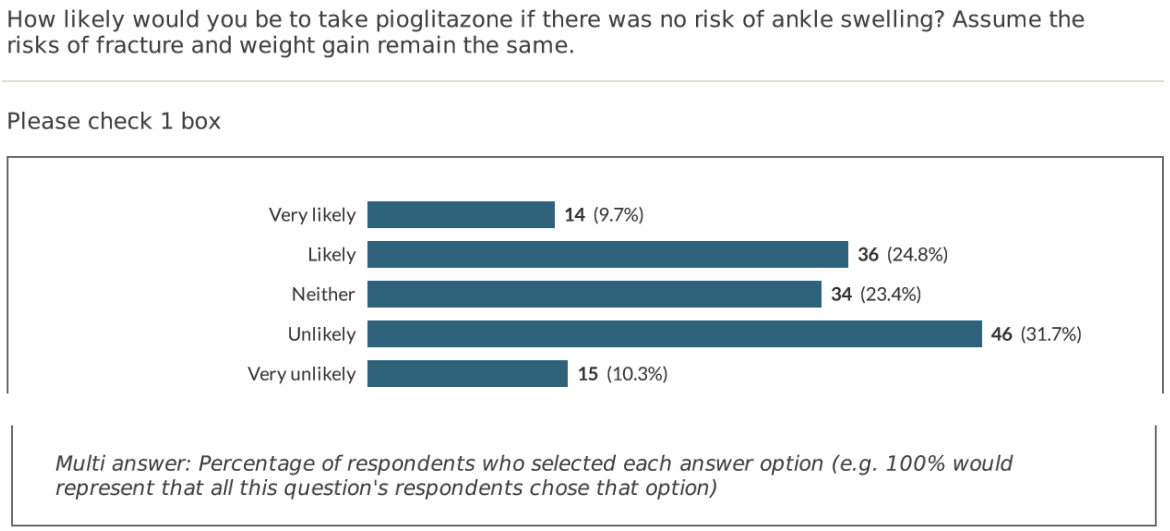

Figure 4-9. Stroke survivors' views if there was no ankle swelling SEs associated with pioglitazone use

Forty-six (32%) of the stroke participants were willing to take pioglitazone if there was no increased fracture risk compared to 69 (48%) who were still unlikely/very unlikely to take it due the risk of fractures (Figure 4-10).

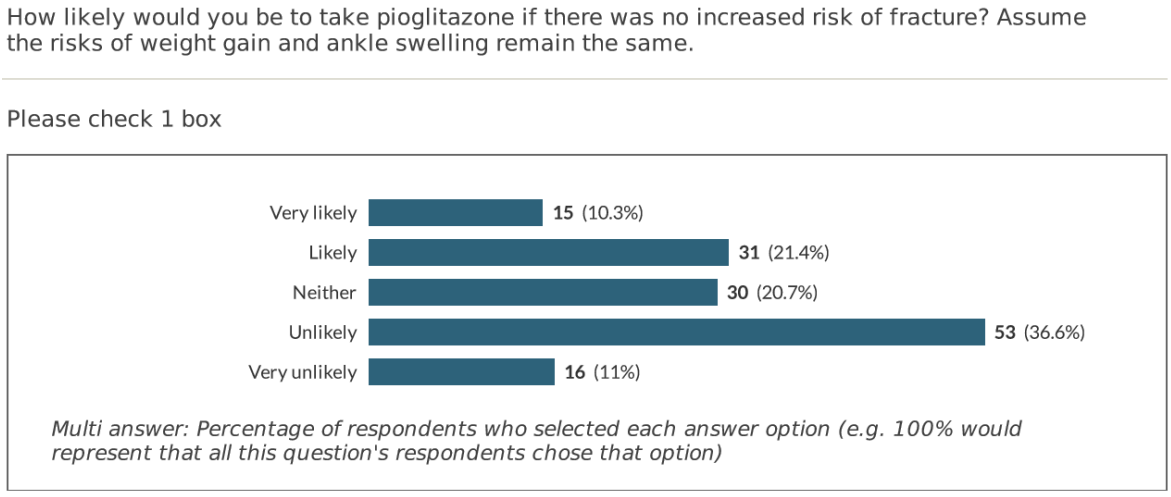

Figure 4-10. Stroke survivors' views if there were no fracture SEs associated with pioglitazone use

That said, 60 responders (42%) indicated they would be likely/very likely to take pioglitazone if fracture SEs were prevented with the use of calcium, vitamin D, or bisphosphonates compared to 65 (45%) who were still unlikely/very unlikely to take it (Figure 4-11).

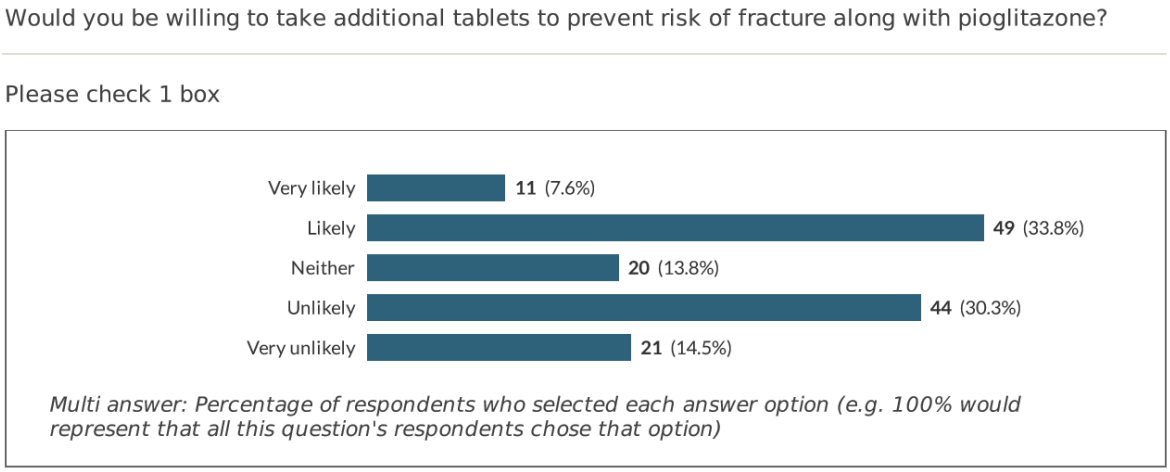

Figure 4-11. Stroke survivors' views on preventive treatment for fractures SEs associated with pioglitazone use

4.3.4 Willingness to take pioglitazone or to participate in further clinical trials

A total of 108 survey responders (75%) supported further research versus 32 (22%) who felt we should discuss using pioglitazone with patients now. Five respondents (3%) suggested we should not perform more research or use pioglitazone at all (Figure 4-12).

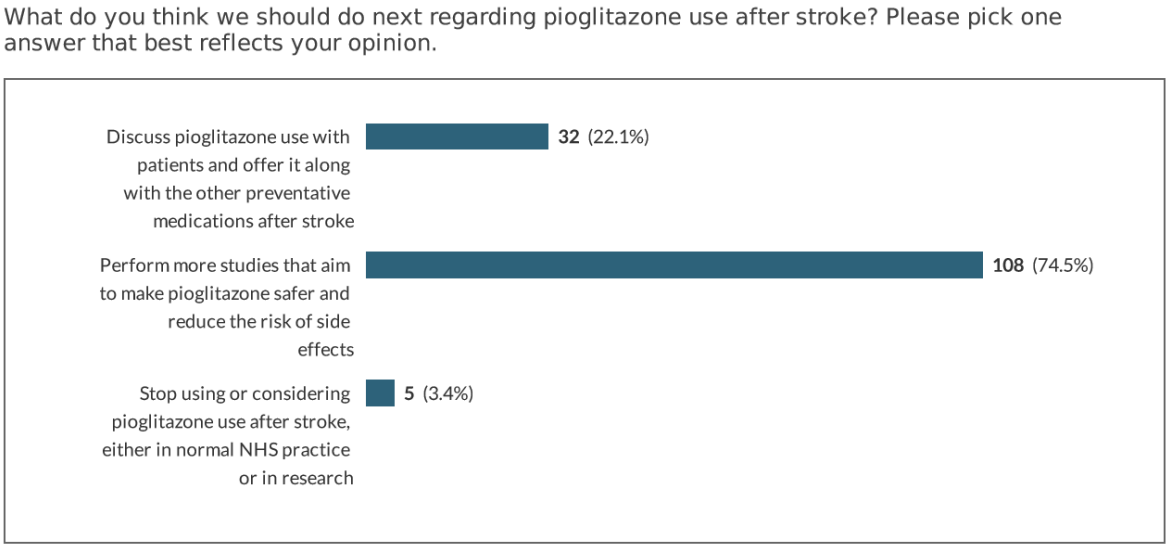

Figure 4-12. Stroke survivors' views regarding the next step of pioglitazone use after stroke

Of the respondents, 59 (41%) replied that they would likely/very likely be willing to participate in a clinical trial that sought to make pioglitazone use safer for stroke patients, while 59 (41%) indicated they would be unlikely/very unlikely to take part. The remaining respondents (27 (18%)) reported that they were unable to decide whether to support such a trial (Figure 4-13).

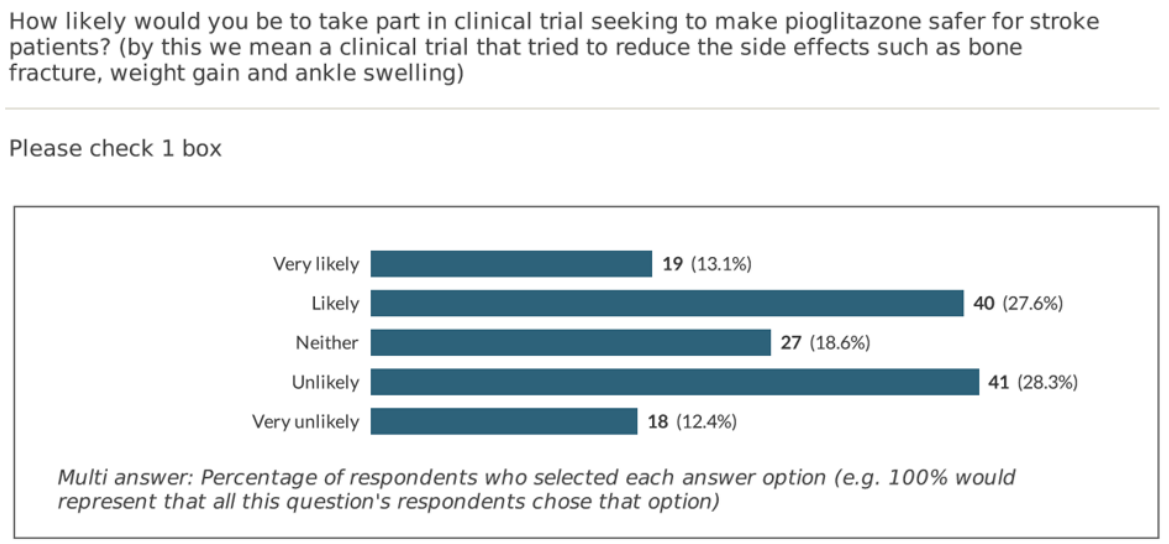

Figure 4-13. Stroke survivors' views on willingness to participate in pioglitazone clinical trial

4.4 Discussion

The results of this UK-wide online survey indicated that stroke survivors have concerns regarding the post-stroke use of pioglitazone. It was clear that participants felt a clinical trial aimed at refining the risk/benefit ratio would be beneficial.

The main findings from this survey were that stroke patients were as concerned regarding pioglitazone use as they were regarding stroke or MI recurrence. This suggests that they place at least equal value on these outcomes. Overall, the patients did not support the routine use of pioglitazone after stroke but did support further research to refine the risk/benefit ratio. This can be done in several ways. Pioglitazone-mediated weight gain can be mitigated when appropriate measures are taken. Indeed, the initiation of lifestyle changes can diminish such gain [421] [422] or even drive weight loss. [423] [187] These measures may also be of benefit after stroke by reducing hospital stays, [424] improving independence and reducing the risk of functional deterioration. [425] [426] [427]

The effect of fall-prevention efforts and strategies to minimise bone loss warrants further investigation. In the IRIS study, most fractures were likely to be related to falls and not all of those events were likely to be pioglitazone related or associated with hospitalisation [141] or weight gain. [416] Interestingly in the IRIS study, a few patients who suffered falls were on vitamin D (19 to 22%) or osteoporotic (2 to 3%) preventive treatments. We envisage that pioglitazone may therefore offer a better risk/benefit ratio early post-stroke if followed by preventive anti-osteoporotic modalities, [428] [429] [430] [431] [432] [433] [434] at least for the first six to 12 months after a stroke, which mark the highest critical period for post-stroke falls and thus would be promising. But this cannot be concluded at present. Most pioglitazone trials [140] [141] [146] did not monitor the incidence of fall-related stroke disabilities, a major risk factor for fractures. This study suggests that stroke participants would be keen to consider pioglitazone in the future if such measures reduced fractures risk.

Some stroke patients have concerns about pioglitazone-associated SEs with regard to participating in future trials. Their perspective may differ, though, when confronted with previous experiences of stroke, TIA, heart failure or fracture. We attempt to predict the rate of stroke participants by their baseline characteristic. Therefore, to reduce the chance of heterogeneity that may arise in comparing those of unknown positive versus well-known negative SEs of pioglitazone. We noticed that those with previous history of stroke seem keen to accept pioglitazone for cardiovascular and stroke recurrence prevention. We also noticed that those with previous unfavourable experience with fractures or heart failure seem to be unhappy with accepting pioglitazone due to its associated SEs. We noticed as well that a minority of the survey participants (27 respondents (18%)) were unable to decide whether they wanted to take pioglitazone. This low response rate may have resulted from their previous history of having a mini stroke (TIA) that has decreased their interest in taking pioglitazone. This is in contrast to those with previous experience of a stroke-related severity

(such as previous history of stroke) or fracture-related disability (such as previous history of fractures, osteoporosis or falls) who seem keen to participate and take pioglitazone if the associated SEs are mitigated.

This is the first study to survey the views of stroke survivors regarding post-stroke pioglitazone use. These findings may inform the design of future clinical trials. The design of this survey, however, had several limitations. Although it was anonymised in an attempt to reduce bias, the risk of 'volunteer bias' may exist. The degree of concern regarding pioglitazone benefits and risks may correlate with an interest in taking part in a clinical trial. This may be particularly relevant to people who experienced severe strokes or fracture-related disabilities. Such histories would be more likely to affect answers or influence participant reasoning than for those without such experiences. Given the complexity of the treatment decisions, the multiple-choice answer options were kept short to ensure the survey was easy to complete. This may have caused some responders to answer in an over-simplistic manner. The response rate was modest, and two-thirds of the responders were males. Both of these factors may have influenced our results. In this online survey, the response rate may have lowered based on whether one survey topic was more sensitive than another or because of the difficulty in gathering a target sample group when surveying the general public. Given the short 10 weeks period we had to complete the survey, the "no response" bias may have increased. Also, because we reached our planned target sample of more than 100 participants, we did not send a reminder email to prompt non-responders to participate in our survey. This decision may explain, in part, the low response rate of 28% in our survey. However, the response rate is consistent with that seen in previous studies within SHARE. This was also a UK survey, so the results may not be generalisable to other European and non-European countries.

4.5 Conclusion

This online survey of UK stroke patients shows that stroke survivors have concerns regarding pioglitazone use post-stroke and do not support its routine use after stroke but do support further research to refine the risk/benefit ratio.

Chapter 5 Exploring the Barriers to Effective Co-morbidity Management Post-Stroke with a Focus on Diabetes – The COMPOSEd study. Patients and Clinicians' Views: A Qualitative Focus Groups and Interviews Study

5.1 Introduction

Stroke is a leading cause of morbidity and mortality and is responsible for about 11% of total deaths each year worldwide. [435] The link between diabetes and stroke is well established and diabetes is associated with more than double the risk for recurrent stroke and further cardiovascular events for an individual. [375] [436] Presently, there is no definitive evidence that glucose-lowering therapy improves clinical outcomes in acute stroke. [437] [438] The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study [94] showed that pioglitazone use reduced recurrent strokes in people with diabetes. However, beyond the specific confines of the PROactive study, we do not know if aggressive diabetes management using more commonly prescribed medications such as metformin or insulin conveys stroke-preventive benefits. The evidence for use of post-stroke diabetes has been enhanced by the American College of Cardiology's Insulin Resistance Intervention after Stroke (IRIS) trial, [93] which demonstrated that the additional use of pioglitazone for insulin-resistant individuals following stroke was beneficial.

There have been many advances in treatment of type 2 diabetes in recent years. In a recent survey of United Kingdom (UK) practice, [417] we found that the post-stroke methods used to detect and treat diabetes are not standardised or routinely implemented. Therefore, because improvements in post-stroke diabetes therapies will take time to translate into routine clinical practice, it is important to understand the current circumstances. Obtaining rich stroke patients data and the thoughts and opinions of healthcare providers will offer important, novel ideas for the redesign of diabetes services and the translation of early-phase research into later-phase research.

The aim of this study is to explore the patients and healthcare providers' views on the acceptability and effectiveness of pioglitazone treatment for post-stroke diabetes management and attempt to identify the barriers to its adoption and understanding the challenges that exist across healthcare networks that contribute to these barriers.

5.2 Methods

The study's protocol was registered through the UK Integrated Research Application System, 238470. [439] Ethical approval also was obtained (reference number 17/LO/2122).

5.2.1 Study design

The study adopted a qualitative approach guided by a 'grounded theory' [440] methodology to inform the conduct and interpretation of focus groups with stroke survivors and healthcare providers. The grounded theory is a well-developed technique for generating a theoretical framework for considering public phenomena in healthcare research. This theoretical approach was deemed most appropriate for this study for, as Charmaz [441] argues, it is an approach most suited to research that explores the thought processes of those involved which cannot be predetermined and are central to its understanding. In taking this approach, we adopted the famous dictum 'all is data' [440] regarding the data generated via the focus groups but also from materials relating to post-stroke co-morbidity management. These materials included, but were not limited to, patient leaflets and clinical guidelines. In this manner, we could inspect all available sources related to post-stroke co-morbidity management.

5.2.2 Study approach

The research with stroke survivors explored their views on the links between the aetiology of stroke and diabetes and how they viewed the acceptability of pioglitazone treatment for post-stroke diabetes management to minimise its associated weight gain and fracture side effects (SEs). Regarding healthcare professionals, the focus groups explored the barriers associated with diabetes co-morbidity management pre- and post-stroke and how they viewed the clinical applicability of pioglitazone in attempts to mitigate its associated SEs and to improve clinical practice in diabetes co-morbidity management pre- and post-stroke.

5.2.3 Focus groups and participants

The interviews were conducted with patients and healthcare providers in two health board centres, one in Scotland and the other in South Wales, through researchers experienced in qualitative methodology. Stroke survivors who had been diagnosed with diabetes, before or after their stroke, were identified through the clinical care teams in the hospitals at both sites. To achieve a maximum range of sex, age, socio-economic status and disability, purposive sampling was undertaken. Within patient groups, we obtained a minimum of two individuals from each gender. Healthcare providers were approached through professional networks and as members of special interest groups. Within healthcare professionals' groups, we aimed for a minimum mix of two stroke consultants, two diabetes specialists, two occupational therapists, two general practitioners and two clinical nurses. These primary and secondary

professionals were all specialising and directly involved in caring for people with stroke and/or diabetes. The final number of interviews was determined by the point of data saturation. [442] Stroke survivors and healthcare providers took part in separate focus groups, consented (Supplemental Figure 5-1 and Supplemental Figure 5-2) and received an information sheet (Supplemental Figure 5-3) to be approached.

5.2.4 Format of the focus groups

The focus groups were structured to provide an opportunity for in-depth investigation of the participant's personal perspectives. Focus groups were conducted in neutral territory away from the patient's home or hospital in what was aimed to provide a 'safe space' for the exploration of the topics covered. A topic schedule guided the line of questioning and prompts encouraged further discussion. Discussion topics were facilitated by asking the participants a series of open-ended questions with which to share their perspectives regarding pre- and post-stroke diabetes knowledge and management at primary and secondary care units. Participants had an opportunity to respond individually and to interact with other participants in an unstructured discussion at the end of each session. All interviews were digitally recorded at the time of the focus groups and were then transcribed in preparation for coding.

5.2.5 Data analysis

To ensure a reliable interpretation, transcripts were initially read by one of the researchers involved in conducting the focus groups to resolve any inaccuracies that occurred through the transcription process by listening to the recordings. The audiotaped interviews were then transcribed verbatim, anonymised, and coded to manage and code the data for analysis. The transcripts were analysed adopting a grounded theory approach. Subsequently, a constant comparative analysis [443] approach identified key points from the data and coded them individually.

An iterative process of data collection and analysis was undertaken. Initially, chunks of data were coded. [444] One research team generated these coding procedures individually and then cross analysed and circulated to the other research members, who scrutinised them collectively to assure the rigour and consistent approach transparency of the data coding process. The coded data would comprise either phrases or large blocks of text that characterised the participants' comments regarding their knowledge and management of pre-

and post-stroke diabetes co-morbidity. The data responses obtained were grouped individually into similar concept categories to identify key themes and subthemes. This was done by H.A. As groups were compared further, more abstract categories developed until core themes emerged at each focus group. A process of identification and refinement of categories followed. This process went through several iterations until the team agreed on a final set of codes. Inconsistencies were resolved through discussion with a third experienced researcher until a consensus on the final themes was reached.

In writing this article, we followed the COnsolidated criteria for REporting Qualitative research (QOREQ) checklist [445] to facilitate the appropriate use of this study in decision-making.

5.3 Results

Three focus groups were conducted (one meeting with stroke survivors and two meetings with healthcare providers) between February and July 2018. The group sizes ranged from four to eight participants and the interviews lasted 45 to 90 minutes. In total, 19 people were recruited from stroke survivors and healthcare professionals. In the stroke survivors' focus group, eight participants from Glasgow, four females and four males who were recovered from stroke and had diabetes and high blood pressure, age was 53 to 69 years. The healthcare professionals' focus group contained two geriatrian/stroke consultants, two stroke trainee doctors, two general practitioners, two diabetes specialists, one occupational therapist and two clinical stroke nurses from Scotland and Wales.

Three themes and two subthemes were identified by stroke survivors and four themes and two subthemes were identified by clinicians. These were isolated by the study's researchers from the participant responses that contributed to our exploration of participants' barriers to effective pre- and post-stroke diabetes co-morbidity management.

5.3.1 Stroke survivors

5.3.1.1 Lack of patients' awareness of the aetiology of stroke and diabetes

Stroke survivors were aware of the possibility complications of diabetes before they had their stroke but were frustrated to learn that the onset of diabetes is often attended by another stroke or a heart attack.

'I`m not aware of a diabetes threat. If it concerned me, it would deal with medication'. ... 'I`ve never linked to stroke'. 'Diabetes causing circulation, amputations, kidney problems.' 'How would I know if I had diabetes?'... 'I discovered as a result of my heart attack, they said. ... "Oh, you've got T2DM ... don't know your sugars because." "My uncle died of a heart attack. He had a stroke, was diabetic ... didn't put (it all) together. I should have because he had ...' (Stroke Survivors Scotland)

Participants cited several examples of their experiences monitoring diabetes. Some participants were positive about monitoring their blood-sugar and already knew that consuming high-sugar foods was an important risk factor for diabetes before a stroke. They realised that, with diabetes, they needed to self-monitor their blood-sugar levels and watch their diet closely.

'If I'm concerned, I manage. I just had three chocolate Easter eggs; it'll go up. Then, when I fast, it'll come down'. 'Before my stroke, I was aware I shouldn't eat chocolate. Most people who have diabetes ... trying to cut back sugar ... ' (Stroke Survivors Scotland)

Other participants were surprised to learn that they had diabetes and stated that, after learning about it, they had not worried about blood-sugar monitoring until the diabetes was complicated by a stroke.

' ... don't self-test. ... Then on we go, have a stroke, recover from a stroke. Nobody at the start said ... What can you do? ... Unless your diabetes got really bad, you`re insulin-dependent. My GP said, "Are you living on jelly-babies?' My blood sugar was so high. ...' 'Anything sweet, never rationed myself before a stroke. I still like them, but I believe it's true ... not just in case you have diabetes should you cut down sugar. If you're taking in an awful lot of sugar, it can ... actually cause a stroke'. (Stroke Survivors Scotland)

The stroke survivors were uncertain about whether they had been tested for diabetes at a hospital or clinic following their stroke. However, a minority of them were aware that their blood sugar was monitored at the clinic annually.

'Haven't had any monitoring'. ... 'The only thing I'm aware of was when I had a review with a GP once a year'. ... 'My blood sugar, weight and blood pressure were monitored by the practice nurse twice a year'. (Stroke Survivors Scotland)

5.3.1.2 Lack of patients' knowledge regarding advance post-stroke diabetes treatment

Stroke survivors did not know that new treatments were available for diabetes management, one that decreased the chance of stroke even in those without diabetes. Once informed that a drug could reduce the likelihood of someone having another stroke by 24%, all participants

were quite interested and excited by this but also wanted to know if any SEs were associated with such treatment.

'depending on what stroke I had, the likelihood of having another… I rather think about that first, but yes' … 'I'a like know more about … SAEs'. (Stroke Survivors Scotland)

5.3.1.2.1 Diabetes and weight gain risk awareness and willingness

The survivors stressed that they had not been aware of the SEs associated with diabetic treatments, particularly weight gain. They also noted that their post-stroke weight gain had adverse emotional, physical or mental effects on them.

'I put on loads of weight since stroke. I lost it, … being exhausted all the time …try to go to classes, … getting my mobility better. Then I`m not all right with a stroke. It throws you back again'. 'I was told when you're tired, … lie down. You'll feel better'. 'Then you get lazy'. 'Putting more strain on the heart. It could restrict mobility, wouldn't like'. (Stroke Survivors Scotland)

Stroke survivors were reluctant to decide about starting the new treatment based on their previous stroke-related disability. Some of them were shocked or disappointed to find out that they would have to learn to manage their stroke-related disabilities incrementally when they transitioned from acute hospital care to living independently. However, regarding the new treatment, those with more severe stroke experiences seemed more willing to risk gaining weight than those with less severe strokes and better prognosis.

'Your own mind would be, well, going to manage weight, almost like diet, exercise, gyms, just to compensate. If you want to make yourself better, you must lose weight and do all the rest of it, balance one against the other'. 'Everybody in a situation like that tries to lose weight … would work at it but would high for some, low for others' … 'would be too much to ask somebody who's just back recovering from a stroke'. 'It takes so long to deal with the shock of the life-changing experience that just happened. Everything has been over. … It's hard enough'. (Stroke Survivors Scotland)

After learning this, we attempted to explore their views on how much of an SE weight gain would be unpleasant for them. Some responded that they feared that a weight gain of a stone and a half (10 kg) would put them at a higher risk of having their mobility restricted. Some participants felt that the treatment benefit of greater stroke prevention would leave them with a better quality of life, which somewhat alleviated their weight gain concern if there were alternative modalities to mitigate the increased risk of weight gain.

'I would do anything not to be overweight. … wouldn't consider drugs if I knew I`m going be overweight … if I put a half-stone on, I would quite happily take it off again so that really freaks me out'. … 'You'd find a stone and a half alarming, but you'd say, "Can I manage weight gain and keep pills?"' … 'What's "alternative", then? If somebody said, "This drug will help, but you're going to put on a stone, but you're never going to take it off, but it's going to give you another 10 years". … 'Better to manage that than manage after-stroke effects'. … 'Bit heavier … but, still, being here beats the alternative'. (Stroke Survivors Scotland)

We emphasised that the post-stroke mobility obstacles the survivors would encounter would be more manageable if the treatment-associated weight gain was monitored with professional healthcare assistance. That is, their GPs could arrange with the NHS to monitor them for early signs of weight gain and provide instructional peer support to help them take good care of themselves and focus on their capacity for optimising their lifestyles through balanced diet and exercise along with encouragement from families, friends and/or spouses.

'It's not about diet; it's about diet and mobility. They have to go hand in hand to lose weight effectively … balancing that'. … 'A doctor's going to say, there's ways (that) will motivate you … when get to stage that you've had a stroke and you're getting better, it gives you more … opinions on it to make you go and motivated to do it if you want. … There will always be people who won't, but if people want to motivate themselves with a doctor's words, great'. … 'Would have thought post-stroke … a lot of self-motivation considering what I had before, but it just wasn't there. Try as I might, I couldn't. … I want there to be weekly at least that kind of clinic, gym to help, because I would find the motivation because I try really easily really difficult, but if I had professional help, doing it, encouraging myself, would make that easier'. (Stroke Survivors Scotland)

Paradoxically, some stroke survivors seemed to look for formal instructions from healthcare that allowed them to passively adhere to professional recommendations rather than engage in the active self-motivation required to understand the rationales behind the recommendations. Hence, we worked to develop their expertise and to establish a harmony and concordance between the patients and the healthcare professionals.

'We instantly jump to the NHS to provide answers but should look at ourselves first … having somebody help … look at yourself before you jump to someone to do magic'. 'How you live life, trying to manage it all together rather than saying'. … 'It's about smoking if you smoke, family … other pressures … looking at your lifestyle rather than getting a half-stone off'. 'If somebody really convinced me 10 years before, "Don't smoke, and you won't have a heart attack", I would've stopped. If somebody said, "Take this pill, and you won't have a stroke", I'd bite their arm off to go after it'. … 'I'm one least affected by a stroke. … I don't want another. … I'm concerned about diabetes sneaking up on me. … I don't know how to cure it … just stop eating sugar?' (Stroke Survivors Scotland)

5.3.1.2.2 Diabetes and fracture risk perception and willingness

The stroke survivors had a diverse range of fall experiences and were unaware that their risk of suffering a fracture was somewhat increased post-stroke. Some felt lucky to have survived

their stroke, even with their recurrent falls. However, for others, falling was a painful experience that affected them adversely, even with fracture-prevention assistance.

'I'm surprised I haven't broken anything. I fall all the time, but I didn't know there's more risk of fall and chance of fracture post-stroke'. ... 'You've got humerus ...everything from council. I press an alarm at home for falls; I fall a lot. I lose balance going from room to room. Put your hand up, down you go, on the floor; you can't help yourself'. ...'When I fell, I broke my hand. The nurse said, "Look at your bones". They're like tissue paper and take nothing to snap, which is why I've broken my ankle. It's a nightmare, broken bones ... all pain ... the mobility side of it. I've been diagnosed with osteoarthritis in my hips ... since the stroke'. (Stroke Survivors Scotland)

Of those disabled by fractures, some survivors felt helpless and pessimistic. In this regard, they felt more anxious about having another stroke that might disable them temporarily or permanently than they did about a fracture that would heal with time. Those who had been reflecting on their history of fractures seemed more willing to take the risk associated with new treatment than those who had not experienced a fracture.

'A fracture will mend with treatment. You can build up strength in physical things, but the stroke left a weakness that – nothing's coming back for the brain to send messages. It's totally life-changing overnight. ... (One second,) you're at work, the next, lying in a hospital bed. Your life has changed. You'll never work again, drive ... automatically think I didn't want a stroke, breaks a leg, ... then you get to those who don't know how bad ... a stroke is, a break is. A break's a break'. ... 'You can have quite a minor stroke, quite a serious fracture, but generally, a stroke's worse'. ...When you say fracture, somebody thinks, ... falling ... a fractured arm, those levels are like levels of stroke. They're not easy, ... like it or not'. ... 'I wouldn't like it either, but a stroke is devastating'. (Stroke Survivors Scotland)

As one possible fall-prevention practice, some participants engaged in risk assessments wherever they went. They also tried taking secondary preventive courses to help them cope with their disabilities, especially their strength and balance limitations, in their own environment. Such skills are difficult to adopt even with the help of a rehabilitation trainee, therapy exercise or consultations on falls with a specially trained nurse.

'Move things out of the way that's going to obstruct me. ... I skip over things, fall, even with plenty of room, get away from rugs, stuff like that'. ... 'My sight to the left's really bad. ... I catch a foot, and down I go. The physiotherapist suggested going to a strength/balance class... to try to avoid falls. The consultant says, "I'm going to send the falls nurse to you". ... They tried for weeks, ... but I couldn't kneel to get up. ... They teach how to get up if you fall, but it just isn't happening. ... If I'm down, ... somebody has got me up'. (Stroke Survivors Scotland)

To help ensure success, such activities should go hand in hand with a flexibility programme and motivational efforts. One suggested strategy to counterbalance fracture risk was to explore the participants' thoughts on the adjunct medical treatment with bisphosphonates. Some found it difficult to accept this treatment. They seemed frightened

of taking on more polypharmacy, as post-stroke-related disability left them with swallowing issues, even if such alternatives would mitigate fracture risk and minimise the chance of future strokes.

'…more drugs always scary…got stuck in throat…"'I take many tablets, can't take anything else…I went from 1-to-15…struggle, …difficult to swallow…choked me…got worse since stroke.' 'If guarantee you're not have another stroke?"' … you'll get balance…If take this, …What get away with? … how I`ll able to cope, if I don't take this, where I`m heading? … question of balance, relying on person talking to you, doctor works out that balance, …take this … this goes-down, … be in perfect weight, but might have stroke…" (Stroke Survivors Scotland)

5.3.1.3 Survivors' decision-making

Stroke survivors were quite satisfied to participate in future trials that involved a drug that might lower their stroke recurrence. However, they were more concerned about weight gain than fractures. Regarding their fractures, their preference was to have a bone scan before and after the study, which seemed a crucial factor regarding their decision to participate in such trials.

'Biggest worry…'weight gain" … I could deal with fracture…no problem.' 'ask your GPs get bone-density-scan, … not unpleasant experience, … after x-rays, nurse will be explained, … how bones made, how stop producing after age 30 … made you more aware … if needed put you on drug…' (Stroke Survivors Scotland)

5.3.2 Healthcare professionals

5.3.2.1 Barriers associated with diabetes co-morbidity management pre- and post-stroke

People with TIAs might experience some cognitive or mood deficits depending on their level of physical decline or their mental state. In the rehab phase, if the ischaemia progresses and becomes associated with diabetes, this can create a barrier to the healthcare providers controlling the target HbA_{1c} level and to the patients adhering to treatment.

'It's very challenging when newcomers who have swallow problems take that NG into the mix of problems for diabetic patients. Suddenly. treatment becomes very complicated. … In the rehab phase, a lot of them are less familiar with … management trying to discuss and provide input in that phase. If they're 230, get dehydrated, drowsy, and therefore don't, their optimum is kind of an initial-phase problematic. Suddenly, that whole tightly controlled … goes out of the window … making sure don't have problem with their ability to take part in rehab. My target difference, compared to the discharge target, is in the low teens. Below that is a risk when they go home'. … 'No clear-cut guidelines'. (Geriatrician/Stroke Consultant, Endocrinologist, Wales)

The primary healthcare professionals and stroke trainees emphasised that the stroke survivors' blood sugar was not being monitored acutely post-stroke and that the regular detection of HbA_{1c} before or after the onset of diabetes was insufficient. These circumstances might challenge the professionals due to the increase in stroke survivors' hospital referrals because of the shortage of diabetes nurses, their lack of a trainee programme and practical experience, or the complexity of fasting glucose-test organisation.

'We looked at it in our unit. Recently, we weren't great with the HbA1c, quality project, screening how many folks had glucose checks. The vast majority went home without them. The issue is, if we pick up, we pick up quite a lot'. … 'It's a challenge getting enough diabetes nurses. We're working hard to train a diabetic team, quite often doing blood tests. We bring them in three months later, but we're not actually changing management. We're trying to intensify our treatment to make sure HbA1c…. "We're treating to target getting patients to comply, and we're picking up more pre-diabetics, even people who don't…look at risk of pre-diabetes. Then you have the whole cohort that needs education, monitoring. We're quite bad doing fasting glucose. Everybody gives random …, and it's difficult to organise fasting glucose …" (Consultant Geriatrician/Stroke, Stroke trainee doctor, GPs, Scotland)

Although people with diabetes were often identified by stroke nurses at clinics, most of these patients were not screened post-stroke or after their hospital discharge with an HbA_{1c} test. Providers proposed that it is crucial to perform such monitoring after an acute stroke. One way to ensure this, if feasible, is to highlight the need for this testing in patients' discharge letter or get them enrolled in a pre-diabetic's health modification programme.

'In the clinic, if an HbA1c hasn't been done, I'll probably order one. But managing it all is difficult. With a new diagnosis, I wouldn't be rushing it as some sort of back-up, nine times out of ten in the acute phase. But if they don't have diabetes, they have poor HbA1c. You start by asking about tablets; are they taking them? ... Maybe what their diet what should be, and mention that in a letter by default, pass it onto primary care. As I'm aware, T2DM management is seen more in primary care than than type 1 in hospital'. … 'Problem is, when people come in post-stroke, no regular check-up takes places. There's no opportunity to come and say, "You've just been discharged after having a stroke. Can you think of anything you need?" It doesn't happen with a practice nurse or GPs. Even a year later, with their check-up with a nurse, I don't think a diabetes screen is done. They do BP, cholesterol. It wasn't on QOF'. … 'I don't think many GPs look at a discharge letter. ... We should see this person, and there shouldn't be barriers, for a one-year review … or financial barriers. It's just not done in this culture. I don't think a stroke one-year review was all that thorough, anyway. The BP aim is 150/90 on QOF, cholesterols, HbA1c would probably be more useful. I wouldn't state that on a discharge letter unless a patient arrived symptomatic and we had suspicions, but not routinely post-stroke'. … 'We have a programme for pre-diabetics, but it has been overwhelmed, with a massive waiting list to get into'. (Stroke trainee doctor, GP, Stroke Nurse, Scotland; Occupational Therapist, Wales)

From geriatric/stroke consultants' point of view, stroke survivors are routinely screened for cholesterol but not specifically for diabetes at secondary healthcare centres. Such monitoring is crucial for elderly patients in terms of starting them on statins early post-stroke if they can tolerate its high dose and to limit expensive referrals to the NHS service.

However, there is no standardised guideline to follow; nor has diabetes testing been shown to identify the high-risk individuals that need post-stroke screening.

'The cholesterol part of an annual review, in a sense, doesn't matter. They're getting started on high-dose statin. They're not tolerant, unless there's familial hyperlipidaemia. You've got an injectable thing that costs millions of pounds checking lipid and doing nothing with it, whereas, think in terms of a black box process, wouldn't it be better to check HbA$_{1c}$ for BP?'(Consultant Geriatrician/Stroke, Scotland)

5.3.2.2 Lack of knowledge of healthcare professionals in relation to post-stroke advances in diabetes management

The focus group for primary care physicians revealed a substantial discrepancy between the optimal approach to managing diabetes post-stroke. Although there was National Institute for Health and Care Excellence (NICE) guidance available on the target HbA$_{1c}$ to follow post-stroke, there was a lack of guidance to support the exact time to check those with acute stroke presentation at risk of diabetes or how to determine whether they had been diagnosed with diabetes post-stroke at the hospital or post-hospital discharge.

'We don't have clear-cut guidelines for HbA1c. If 40 and above is diabetes, depending on the age of patients, the functional level before a stroke and co-morbidities make sure diabetes control is good as possible. Being a diabetologist, my goal differs from a stroke physician's, that is to prevent them from having further strokes because diabetes is the starting point for strokes'. … 'An initial assessment should be able to look at the BM part of neurological assessment. In the case of an acute stroke or high BM, undertaking stress hypoglycaemia. It's viewed as an insulin deficit because of body stress. We can`t due to a stroke but due to illness. If there's no history of diabetes or pre-diabetes, an acute stroke maintains between seven to 12. Post-discharge needs to do glucose tolerance, with fasting blood sugar later, in the rehab phase'. (Geriatrician/Stroke Consultant, Endocrinologist, Wales)

The focus group for stroke consultants highlighted that diabetes treatments appeared to vary from clinician to clinician within the primary and secondary care sectors and even within the same care centre. A central problem shaping this behaviour is that every patient presents with different characteristics and that no universal rule of thumb existed for diabetes management when diabetes is complicated with cardiovascular disease, including stroke. This makes diabetic combination therapies difficult to manage, as they demand more time and resources.

'The issue is, we pick up quite a lot of new diagnoses of diabetes when they come with a stroke. Management simply 10 years ago gave them metformin, and your job was done. There are many variations now, and we struggle to keep up with them'. … 'How should we personalize that?' … We've got two thoughts when people become inpatients. Is this person persistently hyperglycaemic in the ward? Do they have osmotic symptoms? I would introduce treatment to control prior to discharge, then get one eye on cardiovascular risk reduction. Metformin is still at the centre'. (Consultant Geriatrician/Stroke, Scotland)

There was some disagreement regarding the selection of a post-stroke antidiabetic treatment across practitioners. Their preference ranged from sulfonylureas for those with an acute presentation of uncontrolled glycaemia to metformin ± DPP4-Is for those who needed long-term management. The nature of the disagreement differed with the severity level of glycaemia. In general, their guidelines depended on the treatment consultants' preference, their diabetes management post-stroke experience or the primary care location. Such diversity in treatment choices reflects the complexity of diabetic drugs and perhaps highlights the use of these new antidiabetic cumulative SEs' profile for long-term use, the polypharmacy argument and the rapidly growing advances of clinical trials that require professionals to update their practice regularly.

'There is guidance, but it's not familiar with all parts of the problem. My practice nurse does most of it; I'm quite deskilled. We use metformin, lot of sitagliptin, but wouldn't necessarily'. … 'If the patient has osmotic symptoms, really high glucose, we want to keep that down, gliclazide. Beyond that, we need a little bit of education'. … 'In hospital, we use gliclazide, then refer patients to get them tidied up'. … 'Metformin is still at the centre of use, with BP discussion, because we're starting at least three drugs to reduce it – that's four drugs with SEs – in people a bit less well if they've been in hospital long enough. If they're stable over a few weeks, we pass them to primary care and think about metformin'. … 'It seems to depend on where you are. … There's a lot of local guidelines. Metformin's first, followed by gliclazide, then whether alogliptin is used. It comes down to local consultant preference. I don't know what the evidence is or what should be best'. (Geriatrician/Stroke Consultant, Wales and Scotland; GP, Stroke Nurse, Scotland)

5.3.2.3 Pioglitazone clinical applicability and future perspectives

The debate over glucose-lowering therapies for stroke prevention is complicated. The use of pioglitazone was questionable, but it did reduce the net cardiovascular mortality and stroke risk compared to sulfonylureas. However, it seemed challenging to convince practitioners to start to treat people with diabetes post-stroke, perhaps because it might cause associated SEs. In similar fashion, sulfonylureas had negative cardiovascular impacts within a long-term period, but even with such unfavourable aspects, it is still on the market. However, metformin, empagliflozin and semaglutide were not as compelling for decreasing stroke endpoints as pioglitazone. Hence, selecting a combined therapy can be difficult for practitioners due to their lack of practical expertise regarding such newly emerged drugs.

Thus, it will take more research to increase confidence in using pioglitazone. Determining its long-term safety profile seems an important, high-priority step.

'Everyone around the table seems to prefer antibodies to pioglitazone, if you're going to do all that stuff. People are a bit circumspect about using'. ... 'Thinking about the polypharmacy of low-hanging fruit, what to take away first, what to stop if it's telling. There are too many tablets, a lot of work to make it available, make people comfortable prescribing it routinely'. ... 'With diabetes management, patients don't buy it fully. It's difficult to sell them a drug that has all those SEs. Primary care isn't keen to prescribe it anymore'. ... 'It's difficult enough to get a patient to take metformin. If gliclazide came on the market now, it wouldn't get licenced. It's a very nasty drug, but it drags down blood sugar'. ... 'Commonly, stroke people are elderly. We're not aggressive in sort of keeping sugars low'. ... 'The famous cardiovascular benefits of metformin are impressive, but it's ... just kind of hive knowledge.' ... 'If we're running >12, with osmotic symptoms, dehydration and hyperosmolar, but it isn't best for achieving what we're looking for in the short-term concerning reassurance, maybe more weeks aren't good enough'. ... Many GPs feel deskilled and uncomfortable prescribing empagliflozin or semaglutide. Everybody likes metformin, and Sitagliptin now is more common. Generally, I don't like to prescribe things that come from secondary care. Maybe they become familiar, but initially are quite difficult. Many new drugs come on the market, and it's quite hard to stay on top of them all'. 'Even in a very competitive market, insulin and many different drugs keep changing, and it's hard for us'. ... 'Pioglitazone, probably people are a bit more anxious than others'. ... 'I wouldn't see myself prescribing it unless there are a lot of bigger numbers, longer-term safety follow-up, and a drug with attendant consequences wasn't anticipated in initial trials. I don't want to sound too pessimistic, but I'm thinking about hypertension and diabetes, the stroke population changing. It's older people with three to four strokes, lots of comorbidities. I wonder if trials are moving things way forward'. (Consultant Geriatrician/Stroke, GPs, Scotland and Wales)

5.3.2.3.1 Weight gain and fluid retention preventive strategies

The feasibility of using pioglitazone for people with diabetes and stroke was questioned by the focus groups of healthcare providers. We attempted to explore their views and learned that they were afraid to use pioglitazone due to some intensifying speciality bias that associates pioglitazone with weight gain or fluid retention. If there were some favourable effects from using pioglitazone that would eliminate the negative impacts of the different drugs used in diabetes co-morbidity management, it would promote polypharmacy compliance.

'If they're taking tablets but think they're gaining weight, does that affect their compliance? Once they go home and start feeling better, they think, I won't take my medication today, and they start playing around with it'. ... 'My trials were reading quite bad; individuals are different. Some very select individuals I could make a case for it, but because the cardiovascular comorbidity rate is so high and undiagnosed rates of CHD and LVSD reasonably high, HF... we have other treatments that work, that are anti-hypertensive. There's this idea that pioglitazone lowers BP; is that really doing a lot for diabetes or just giving an anti-hypertensive effect? If we try to add another, are we going to have them not taking something else? Hence, the polypharmacy argument'. ... 'The incremental benefit we seem to get isn't great. There are other things in our toolbox we can use for diabetes. They're probably going to get amlodipine. Then, any benefit with pioglitazone is lost because all medications stay in a box'. (Consultant Geriatrician/Stroke, Scotland)

Pioglitazone would be promising for clinical practice if its SEs profile could be mitigated. For fluid retention, one possible mitigation strategy would be to target a population that has not had heart failure (HF) or that has a relatively low risk for HF. This would call for monitoring the early signs of HF using specific blood tests or echo detection.

'It's feasible, but will it be more treatment burden? Giving three tablets for those three SEs of another tablet, that's another four tablets on top of statin, antiplatelets, three antihypertensive, PPIs'. … 'I wouldn't concomitantly be treating with other medicines to prevent SEs, to get them onto, given absolute benefits…being attractive to them. … There may be selected patients who are at risk of complicated HF. I don't see it would be easy to routinely add them to a list, but if you know their heart's in good nick, you want an echo as prerequisite before starting on them relative to other drugs like BNP levels'. (Consultant Geriatrician/Stroke, Scotland)

5.3.2.3.2 Fracture mitigation strategies

From the point of view of occupational therapists, people with diabetes can manage their blood-sugar levels well before they have a stroke. However, they were concerned that the target HbA_{1c} would be difficult to manage rapidly following a stroke. Their decisions on treatment choices were based on clinical judgement that called for aggressive glycaemia control founded on risk factors such as increased hypos complications, low energy, the likelihood of falls, the swallow status and the size of infarct that may keep stroke survivors from entering an early rehapitalisation programme.

'If somebody becomes functionally disabled because of stroke, they have cognitive problems. If they had diabetes before and were managing well, now they can't. If we suddenly make them strictly, super-tightly controlled in the first two months, post-stroke … in hospital in the rehab phase, we have problems. Either we can't have rehab because of recurrent hypos or had them during the night, they're too tired or lethargic, they had a swallowing problem, or they were less familiar with diabetes management. We're trying to provide input in the acute phase, though there are concerns patients might not be able to adhere to their medication once they get home'. … 'Current guidance and implications for older patients is try to go for higher targets, even if they're not as young as stroke diabetics. They're trying to exercise prevention with slightly less tight control with hypos and falls'. (Occupational Therapist, Wales)

The secondary healthcare providers supported the use of physiotherapists after the patient rehab phase because this would help patients improve their functional disabilities through their engagement with and motivation for regular physical assistance and a health education programme. This also would help patients improve their outlook, take greater ownership of their condition, improve their adherence to medication regimes and facilitate subsequent treatment decisions.

'From the patients' perspective, six months, twelve months down the line, that might be helpful for lifestyle change and exercise programmes. It's difficult.' ... 'Is there intervention needed for those people? Do they need more input than they're currently getting regarding diabetes education post-stroke?' ... 'We've got to look at what the failure rate is afterwards. Because as somebody who fails on diets, medications every now and again, it's all about being fully committed to doing something, and some people are, others not'. (Geriatrician/Stroke Consultant, Occupational Therapist, Wales)

For fracture protection, one possible modality to alleviate breaks was a Dual Energy X-ray Absorptiometry (DEXA) bone density scan before and then annually after initiating pioglitazone treatment in selected patients who had not suffered a fracture. This might be achieved through appropriate patient safety counselling and by using early Fracture Risk Assessment Tool (FRAX) scores to encourage the use of substitute preventive therapies as bisphosphonates in those with or at risk of low bone mass. Implementing this would be relatively expensive.

'If they don't fall regularly with a fragility fracture, maybe we could use FRAX to estimate the osteoporotic risk before starting. We tell them we're going to roughly double it. We might not cross the threshold putting on bisphosphonates to go down that route but discuss using them'. ...If I had infinite time and resources to do personalised medicine ... DEXA ... maybe not much... but is that practical? I'm thinking about economics. Is money that plentiful to invest worth a modest gain?' (Consultant Geriatrician/Stroke, Scotland and Wales)

5.3.2.4 Strategies to improve clinical practice in diabetes co-morbidity management pre- and post-stroke

The focus groups' healthcare providers complained that stroke services are too medically oriented and that the flexibility in stroke management guidelines needs to be improved. They suggested that early diabetes co-morbidity detection and post-stroke management guidelines should be modifiable and need to be supported and fostered by policymakers. These guidelines need to be clear, up to date, adjustable over time and easily followed using applicable standardised mnemonic recommendations. Thus, may guide the communication and professional gap across the primary and secondary healthcare systems. These goals would be challenging to achieve. However, yearly diabetes detection and examinations in the primary and secondary sectors with dietician assistance or patient home visits could be appropriate suggestions and would provide an impetus for healthcare providers to act.

'NICE is very woolly, just give the whole option of drugs'. … 'If there's robust evidence and guidelines that are clear, GPs used to adjust their practice with the times. What became problematic was if guidelines weren't current, you can't follow them. Evidence is a bit wishy washy. Things come up all the time, and you have to change your practice. We still don't know about pioglitazone. When something comes out, it's given bad press, and it's difficult for people to get their head away from it. In primary care, there's been a change in monitoring now. GPs practice in clusters, and diabetes is becoming so specialized. Whether having a GP or a specialist is needed and becoming a problem is a minefield. We're becoming deskilled doing it. There's one GP in our practice who's about to retire, and we don't know what's going to happen'. … 'On the flip side, the thing that revolutionised BP treatment was ABCD. If we operationalise for something simple, is what we need? The GGC flowchart is incredibly complicated'. 'It starts with metformin, doesn't it?' … 'It's relatively simple, but tinker with step two when they're inpatients. The basics are simple, with new drugs with which we're less comfortable and we're playing with. We're not happy with sugar but sending them home. Who takes ownership of that?' … 'If it becomes routine that everybody gets an HbA1c diagnosis annually, but it would be fairly cheap' … 'If somebody's found high HbA1c the minute he or she is discharged, it is mentioned in the letter, they'll automatically add it. In primary care, it would be done annually'. … 'Some of the initial patients in secondary care are people who've been diagnosed. The dietician should be available to come, speak with the new diagnosis before he or she gets drugs'. (Consultant Geriatrician/Stroke, Scotland; GPs, Scotland and Wales)

The synergy between a primary care team charged with acute stroke and glycaemia management and secondary services charged with cognitive rehab would be promising. To resolve the issue of NHS staff and hospital space shortages, these goals could be achieved by assigning specialised consultants to GP surgeries for at least one to two days per week or month. In the future, it is vital to discharge patients to their homes rather than to nursing homes and to employ a clinical pharmacologist in the stroke unit who aids the stroke team with decisions regarding drug interactions and in calculating safe dosages, especially for elderly patients with diabetes or renal co-morbidity impairments.

'If there are problems with administering drugs like insulin and anything from a post-stroke function, they should return to secondary care and the stroke specialist'. … 'Finding the right place to control'. … 'In the Cardiff-Vale-Trust, they assigned consultants to GP surgeries. They've saved 81,000£ to 170,000£'. … ''We tend to use eGFR, which was reported by the lab. It's not easy. The computer doesn't calculate it, so you've to do that extra step. It's a much more thorough application than pharmacists do'. … 'We're getting lots false-okay eGFRs. … They assume everyone is 1.7m tall and have a body mass of whatever. … If an 85- to 90-year-old person doesn't weigh much, the eGFR is far lower. We're trying to improve discharge to home, not be reliant on the nursing home for medication administration'. (Geriatrician/Stroke Consultant, Endocrinologist, GP, Wales)

5.4 Discussion

The COMPOSEd study draws together for the first time the opinions of stroke survivors and healthcare professionals across the primary and secondary sectors to shed light on pioglitazone feasibility. In this study, we aim to assess the trade-offs between the desirable and undesirable consequences of pioglitazone as a preventive post-stroke treatment to capture and analyse the barriers to its adoption among provider networks. In doing so, we

hope to provide direction for guideline developers to make informed recommendations based on our findings for clinical use or future studies.

The association between the stroke survivors' perceived risks and their willingness to accept treatment is being viewed equally or more significant concerns. The stroke survivors' view of adopting pioglitazone use is having to choose between better longer-term stroke outcomes or the risk of weight gain and fractures. The behaviour of those reluctant to choose the treatment may resonate with the loss-aversion phenomenon, [446] which refers to a tendency to avoid loss in favour of gaining benefits. The preferences of these individuals are to be monitored by professionals for early signs of SE and to engage in a long-term rehab programme with the caveat of being flexible and sensitive to the demands of their lifestyles. They believe this approach will help them adhere to medication regimes and allow them to overcome their stroke-related disabilities.

The healthcare professional view of the applicability of pioglitazone in clinical practice is neutral. Their perceptions are multidimensional. Some do not have knowledge of advances in stroke treatments, while others avoid pioglitazone due to the greater treatment burden. These problems may be resolved through knowledge, motivation, attitude, practice and outcomes framework. [447] This may involve moving from a state of being unaware to a state of being aware and the process of changing behaviour via communications and recommendations. Although healthcare providers viewed some practical heterogeneity with chemotherapeutic advances in diabetic management post-stroke, their preference is to devise optimal guidelines that combine rigour with flexibility for early diabetes screening in acute stroke patients. At the very least, a recommendation for this screening should be mentioned in patient discharge letters.

This study highlights that participants feel challenged in deciding if they will adhere to pioglitazone regime, given the probability of weight gain, peripheral oedema and fractures SEs. Arguably, a clear approach can address these. However, physicians must consider the abilities and needs of their patients. Despite the enhancements achieved in the IRIS [93] and PROactive [94] studies and the personalised medicine approach used in IRIS, the success in eliminating HF excess risk through a dose reduction or discontinuation in those who develop significant oedema gives cause for hope. However, there is no clear consensus on the optimal approach to mitigate weight gain and fractures with pioglitazone use post-stroke. This makes it harder for stroke clinicians to persuade them to use pioglitazone post-stroke. We think that literature gaps exist, and we have produced strategies to optimise pioglitazone’s use and to

clarify such matters. Therefore, we hope these strategies will help us decide what we must do next to ensure the best treatment is offered.

Weight gain represents a primary anxiety for stroke survivors, while peripheral oedema is a primary concern for healthcare providers, in the views of this study. However, we must understand the mechanistic pathway of these SEs and, at best, how we can eliminate them with pioglitazone use post-stroke. For the weight gain and peripheral oedema SEs with pioglitazone, these may be explained by increased subcutaneous adipose tissue mass rather than increased visceral deposition or overall adiposity. [109] As a result, there is a tendency for fluid accumulation and plasma volume expansion owing to renal sodium retention, [201] which will increase HF risk if the sodium levels are unchecked. [129] However, in IRIS, [198] the participants who gained weight had longer survival rates and fewer HF hospitalisations, improved their glycaemic control and had lower rates of substantial dependency on recurrent strokes than those with a low-to-normal body mass index or those with high HF risk. [448] Whereas in PROactive, [197] notably, HF events independently correlate with increased stroke incidence or mortality rates. We will follow the IRIS [93] recommendation, that is to use safety algorithms to trigger pioglitazone dose reduction for significant oedema. However, where this study varies from such a precision medicine approach is that we aim to target people with the highest chance of benefitting from the prevention of strokes and simultaneously for a low risk of weight gain and peripheral oedema development. We envisage employing B-type natriuretic peptide biomarkers [449] to monitor those at high risk of HF development [450] [451] [452] and an early echo test screening before and after pioglitazone use, by those in whom we hope to counteract peripheral oedema risk, along with a strict caloric diet [421] [422] [423] and exercise [187] with a degree of flexibility to counteract weight gain risk. With these strategies, we hope to alleviate the fear of patients and physicians regarding pioglitazone use post-stroke.

Both focus groups did not consider fractures to be as clinically important as stroke prevention with pioglitazone. However, we need to understand the mechanism of fractures and, at best, how we can mitigate these with pioglitazone use post-stroke. The fractures may be explained by decreased bone formation [167] and increased bone resorption [169] in bone mesenchymal stem cells that accelerate bone loss. [364] In the IRIS [141] and PROactive [140] studies, it is noteworthy that non-serious and serious events were observed in particularly ill patients, the majority of which related to falls. However, neither study measures the frequency of fracture-related stroke disability or provides baseline data on falls,

which are major risk factors for fractures. [142] [143] [152] Interestingly, a minority of IRIS trial participants was on fracture-prevention treatments. Whereas this study aims to target people with the highest chance of benefitting in the prevention of strokes and, simultaneously, the lowest risk of fractures. It is conceivable to achieve that by combining fracture-risk assessment screening to exclude those with the highest risk of fractures/falls [453] using the clinical scores of the FRAX [454] [455] and DEXA scan, [456] with the early use of secondary preventive treatments for fractures [428] such as bisphosphonates [429] [431] and vitamin D. [430] [434] We hope by these would provide specific opportunities to eliminate fractures risk with pioglitazone use.

To understand pioglitazone implications post-stroke, it is crucial to consider why pioglitazone is required in clinical practice. The UK Medical Research Council [457] suggests that the drug's acceptability should be assessed by evaluating such complex intervention, with benefits and risks, as well as variability in individual-level outcomes. From the perspective of personalised medicine, [458] [459] what makes us unique from IRIS is that we aim to do more stratifying regarding stroke patients who do not have pre-treatment SEs and that most likely will benefit from pioglitazone use with a targeted specific time to interfere and a therapeutic dose window. We know stroke survivors are roughly at double the rate of fractures due to falls early after a stroke. [152] However, we are reassured by the prospect of excluding those at the highest risk of fractures at the baseline and using the proposed alternative therapy for fractures within the critical therapeutic window of the first six to 12 months of falls after a stroke. We hope such an approach might allow patients to take greater ownership of their condition and subsequently facilitate treatment decisions and reduce their costs by raising the accurate use of pioglitazone in a selected population. For healthcare professionals, these strategies seem logical, though there were financial considerations raised in terms of their implementation. However, when introducing this compared to the vast NHS spending on complex patients, [460] it would be reasonable to accept these strategies for further multi-morbidity prevention.

Given the European [265] and American [250] guidelines of an HbA_{1c} of <7% for glycaemia control in people with strokes and TIAs, it seems challenging for professionals to detect survivors with HbA_{1c} early post-stroke at primary care centres and to follow the updated clinical trials and the chemotherapeutic advance of diabetes therapies. From thie study emerged data on the implementation of HbA_{1c} in the stroke rehab phase. Whether for diagnosis or ongoing monitoring, this appears, for some healthcare providers, to be a

preferable solution for early co-morbidity detection and management post-stroke. This raises questions over the possibility of detecting missing cases that develop soon after discharge or whether such rigorous screening in normal care can increase their identification and consequently lead to changes in their current management. In addition, if linked stroke-research networks can be implemented, this may decrease the uncertainty regarding the management of stroke patients at risk for diabetes.

The vital ingredient in all of this is education. Education is essential for those in a state of flux between being receptive to adhering to guidelines and rejecting those guidelines, as well as for survivors who would welcome a sense of empowerment in managing their health needs. Given the practice variation that emerged between professionals, it would be instructive to submit this study for audit across services and to instil through clear health education a feeling of confidence in their practice about which patients to treat and when. Likewise, patients need simple guidance to adhere to pioglitazone use. They must be aware of its potential SEs and under what conditions or at what times it should be monitored. Joint decision-making involving patients is shown to increase their likelihood of compliance. [461]

This study has a diverse representative sample of participants in terms of their gender and the range of settings and experiences. With such heterogeneity, some participants may have found their opinions unsupported by others and may not have felt fully able to articulate them. As a theoretical framework for acceptability [462] and to guarantee the best clinical outcomes achievable with the resources available, we combine the insights of stroke survivors and healthcare providers to further explore pioglitazone's applicability. To the authors' knowledge, this is the first such study in the literature. For our sample size, the healthcare professionals were drawn from Glasgow and Wales primary and secondary care centres to increase the probability of diverse experiences. Even though stroke survivors were drawn from Glasgow hospitals and perhaps have more uniform opinions than a more dispersed sampling, we still could identify clear patterns of practice that could inform a trial design. Moreover, using three focus groups (19 participants), the theoretical saturation is assured. [463]

5.5 Conclusion

We need to understand the benefits and risks of pioglitazone use much better. With this study, we have taken several steps in this direction. Further research is needed before

widespread use of pioglitazone to optimise the risk/benefit ratio and to identify people for whom the benefits would be largest and the risk acceptable. The findings of this study confirm the need for such trials. Instituting appropriate health education and allowing flexibility in developing guidelines from the perspective of stroke survivors and those implementing them would be appropriate suggestions to incorporate into pioglitazone post-stroke co-morbidity management.

Chapter 6 The Thesis Summary and Future Directions

Stroke is a significant disorder that causes functional and structural disabilities and doubles the risk of further cardiovascular events. It also has negative impacts on the social and health burden and will increase in prevalence over the coming decades. Following a stroke, over one-quarter of stroke patients will experience another stroke or transient ischaemic attacks (TIAs) within five years of their initial event. Considerable scope exists for the prevention of recurrent attacks. Previous clinical studies had consistently showed that improving glycaemic control in people with type 2 diabetes mellitus (T2DM) had minimal effect, or at best, only a modest effect in reducing stroke. We need better interventions to prevent stroke. Pioglitazone, a thiazolidinedione therapy for treating people with T2DM, has been proven effective in reducing recurrent cardiovascular events in insulin resistant individuals who have suffered an acute ischaemic stroke or TIA by one-fourth. However, the net benefit has been debatable in certain groups of people as pioglitazone increases the risk of fractures, weight gain and peripheral oedema (ankle swelling). This thesis has explored various aspects of using pioglitazone therapy as a secondary stroke prevention via a mixed-method study approach.

Fracture is an important clinical issue with post-stroke pioglitazone use. I conducted a detailed systematic review and meta-analysis of the fracture risk associated with thiazolidinedione drugs following best-practice guidance to better identify the individuals at highest risk for fracture and to inform the risk/benefit ratio for clinical use or further studies. We found that pioglitazone use increases the rate of non-serious and serious fractures. However, these events are predominant in the lower extremities and the majority of them are related to falls. In addition, these findings are mostly driven by studies that compared pioglitazone use to placebo and pioglitazone use in women. There was little data on fracture risk in people with previous strokes. Regardless, these data may raise the possibility that the risk/benefit ratio may differ between males and females and may help stroke physicians decide whether to use pioglitazone in selected patients. It may also inform future clinical trials of post-stroke patients.

There are several new classes of antidiabetic treatments today, some of which have been demonstrated to reduce cardiovascular risk. I conducted a second systematic review and meta-analysis to assess the effects of these new antidiabetic drugs on the incidence of stroke. I found that the use of the dipeptidyl peptidase-4 inhibitors agents did not reduce the non-fatal or fatal strokes. I also found that, although the use of the sodium-glucose cotransporter-2 inhibitors agents may reduce the risk of major adverse cardiovascular events

(MACEs), there was no evidence of a beneficial effect on stroke. However, I did find that the use of the glucagon-like peptide-1 receptor agonists (GLP1-RAs) agents reduced the risk of non-fatal strokes without an evidence of such reduction in fatal strokes. These findings may guide clinicians in managing people with T2DM at low risk or high risk of MACEs and/or stroke. Whether these beneficial impacts would translate differently or similarly if they were initiated earlier in the acute stroke population remains uncertain. None of these newer drug classes target insulin resistance, however. Given the lack of evidence that any new glucose-lowering agents may be superior for secondary stroke prevention in people with previous strokes, the net observed vascular protection with pioglitazone use to mitigate cardiovascular mortality risk, including stroke and myocardial infarction (MI), in people with antecedents strokes and nondiabetics and diabetic is somewhat unique among other antidiabetic drug classes.

Next, I explored the views of stroke patients regarding the use of pioglitazone therapy after stroke and how best to minimise its associated risks in the *PIOSurvey*. Stroke survivors were concerned regarding pioglitazone side effects (SEs) and rated fractures and weight gain. They viewed these as being equally or more significant concerns compared to the benefit of a reduction in second strokes, TIAs, MIs or the development of diabetes. We envisage that if fracture risk is mitigated through the use of bisphosphonates and vitamin D, at least for the first six to 12 months in the early phase of stroke rehabilitation, which mark the highest critical period for post-stroke falls, this could refine the risk/benefit ratio in favour of pioglitazone use. For weight gain, we think implementing lifestyle changes combined with controlled diet and moderate exercise would alleviate such risk. It is clear that however from this survey trials to refine the risk/benefit ratio of pioglitazone use are needed.

I also conducted focus groups to assesses the view of patients, caregivers and clinicians regarding post-stroke diabetes management (the *COMPOSEd* study). Stroke patients appeared more willing to accept pioglitazone-induced SEs if minimised than a higher risk of further stroke-related disabilities. Healthcare providers, in contrast, were more concerned with the pioglitazone-associated SEs and felt there was a gap in their knowledge of the new antidiabetic post-stroke management drugs. It is clear that measures to improve the risk/benefit ratio of pioglitazone are needed to ensure buy-in from patients and clinicians.

A critical question is whether such data will persuade clinicians to begin using pioglitazone post-stroke. At present, this seems unlikely. We have counteracted these

problems by taking steps to ensure that pioglitazone's important benefits find favour with patients and clinicians. However, the validity of our findings from qualitative researches identified novel themes for further clinical trials with pioglitazone use post-stroke and were strengthened and supported by the evidence from our quantitative researches. As such, a mixed methods study approach using triangulation [464] deepened our understanding of the issues related to pioglitazone use post-stroke and gave this thesis novelty. Thus, the findings of this thesis have important health implications.

There are many potential areas for future research. The best way to demonstrate the benefits of pioglitazone might be to target people with the highest chance of benefitting in the prevention of strokes who are at the same time at low risk of fractures and/or peripheral oedema realising the goal of applying precision pharmacotherapy. [269] This can be achieved by selecting a young patient group (insulin-resistant men and women $\geq$18 but <65 years of old) that has the highest risk of stroke recurrence (e.g., acute evidence of stroke or TIA or lacunar infarctions of the small vessels disease within 180 days of an ischaemic infarction) and the lowest risk of fractures (no previous personal or family history of fractures, osteoporosis or falls). This could use clinical scores for fractures risk such as fracture risk assessment tool, dual energy x-ray absorptiometry scans or genetics test screening to select those at high risk of fractures. The use of bisphosphonates and vitamin D could be considered to reduce risk of fractures, along with strategies to reduce falls risk. To reduce the risk of peripheral oedema, we could use B-type natriuretic peptide biomarkers to monitor those at high risk of heart failure (HF) development, that is, those with previous history of ischaemic heart disease who are at high risk given their high body mass index, high systolic blood pressure, high total cholesterol and/or high fasting plasma glucose. An early echo test screening would alleviate such risk.

Other alternative strategies to reduce the pioglitazone-associated SEs post-stroke is the possibility of using a lower dose of pioglitazone (15 mg and 30 mg). This might reduce risk of MI and stroke but cause fewer SEs. It is important to establish whether it is feasible to conduct a trial, which could be crucial to realising the goal of applying the therapeutic receptor theory [465] in stroke and diabetes cases. From the diabetic benefits point of view, such a combination with GLP1-RAs would provide better pharmacological outcomes of glycaemia and HbA_{1c} controls with the possibility to decrease their dose to less than half for each intervention with minimal or no SEs of excessive weight or bone fragility that what are observed with pioglitazone use. We would be suggesting that in people with T2DM who

present with stroke, the use of pioglitazone and GLP1-RAs (dulaglutide) should be considered first as they are at high risk of stroke recurrence. Thus, determining if different classes of antidiabetic drugs would provide better treatment solutions for people with acute stroke at risk of MACEs.

The characterisation of stroke severity also needs to be adjudicated. It is crucial to follow the 2013 criteria of the American Heart / Stroke Association, which defines stroke by type and subtype [466] rather than just using the term *stroke*, which encompasses all non-fatal and fatal ischaemic and/or haemorrhagic strokes. A robust assessment of stroke and fracture outcomes as primary clinical endpoint is needed over an extended timescale (hazard time of fracture-related stroke disability and mortality). It is crucial also to monitor the surrogate markers for fractures as secondary outcomes (e.g., bone formations such as alkaline phosphatase and procollagen type 1 N-extension peptide and bone resorption such as cross-linked carboxyterminal telopeptide of type 1 collagen) before and after pioglitazone use.

Preclinical [92] [103] [104] and observational [467] studies find that pioglitazone use has suppressed inflammatory cytokines and oxidative stress, which are seen following acute ischaemia and chronic cerebral hypo-perfusion. This effect counteracts further brain damage and neurodegeneration, including dementia, in people with diabetes. However, this promising information is not supported by the data available from clinical trials. Therefore, it would be of interest to monitor the inflammatory mediators' post-stroke in our future clinical trial. Our hope is that the proposed strategies would yield valuable information about the slow evolution of stroke-related fracture disability and mortality events that would help us assess the impact of pioglitazone by time and dose.

A critical question is whether any observational studies or precision medicine data is required before starting the proposed clinical trial. After conducting a critical review of the accumulated evidence, we found that all proposed modalities for mitigating the risks associated with pioglitazone use have been previously examined. For the risk of fractures, preventive therapies such as bisphosphonates/vitamin D have been tested individually and in combination on people with acute stroke [428] [430] or at high risk of fracture. These individuals include postmenopausal women with osteoporosis. [429] [431] For the proposed genetic test screening to select those at high risk for fractures, [468] previous research found a relationship between reduced bone mineral density and silent C to T transition in exon six of peroxisome proliferator-activated receptor gamma polymorphism, which was expressed

on the osteoblast of Japanese postmenopausal females. [469] This condition increased their risk for osteoporosis. Whether this genetic association is present only in certain Japanese postmenopausal women is still a controversial question. No clinical trial has been performed on the relationship between this type of polymorphism and bone metabolism in people with stroke or in people with or without T2DM. This would be a novel area for further research. For the risk of weight gain, the implementation of lifestyle changes, combined with moderate exercise and controlled diet, has been tested on people with stroke [424] [425] [426] [427] and on people with T2DM [187] [421] [423] or metabolic syndrome [422] after use of pioglitazone. To mitigate the risk of peripheral oedema, B-type natriuretic peptide biomarkers and early echo test screening have been used to monitor those at high risk for HF development. [449] [450] [451] [452] It remains uncertain however whether using these mitigation strategies, along with early screening modalities using precision medicine, would translate differently or similarly, if initiated earlier in acute stroke population when using pioglitazone in insulin-resistant individuals.

In summary, it is unlikely that individuals will be able to achieve reductions in coronary and cerebrovascular events with other anti-hyperglycaemics like those achieved with pioglitazone. In addition, the risk of fracture, weight gain and peripheral oedema from pioglitazone use may be able to minimise tipping the risk benefit ratio in favour of pioglitazone use in people with insulin resistance after stroke. A clinical trial is needed to test this.

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Appendices

Chapter 2 Thiazolidinediones and Risk of Bone Fractures. A Systematic Review and Meta-analysis of Randomised Controlled Trials

2.1 Search terms details

A computer assisted literature searches were performed using the Cochrane Library, Ovid Medline, Embase, PubMed and Web of Science databases.

2.1.1 Cochrane Central Register of Controlled Trials (CENTRAL)

#1 (Bone fracture* or bone* or fracture* or fracture risk*):ti,ab
#2 (fracture*):ti,ab
#3 (Fracture* or bone*):ti,ab
#4 (#1 or #2 or #3)
#5 [mh ^"PPAR gamma"/AG,DE,ME,PD,TU]
#6 [mh ^"Peroxisome Proliferator-Activated Receptors"/] or [mh ^"Transcription Factors"/AG,DE,ME,PD,TU]
#7 [mh ^Thiazolidinediones]
#8 (("peroxisome proliferator-activated receptor gamma" or "PPAR gamma" or "PPAR gamma" or "PPARgamma" or PPARG or NR1C3) near/5 (agonist* or modulator* or stimulat* or stimulant* or activat*)):ti,ab
#9 (thiazolidinedione* or glitazone* or pioglitazone or rosiglitazone or troglitazone or netoglitazone or rivoglitazone or ciglitazone or balaglitazone or darglitazone or edaglitazone or englitazone or lobeglitazone):ti,ab
#10 (#5 or #6 or #7 or #8 or #9)
#11 (#4 and #10)

CENTRAL search syntax
The 'near' operator defaults to within 6 words;
'*' indicates truncation.

2.1.2 MEDLINE search strategy (Ovid)

1. Bone fracture/ or exp bone/ or exp fracture/ or exp fracture risk/
2. fracture$.ti,ab.
3. exp Fractures, bone/

4. or/1-4

5. PPAR gamma/ag, de, me, pd, tu

6. Peroxisome Proliferator-Activated Receptors/ag, de, me, pd, tu or Transcription Factors/ag, de, me, pd, tu

7. Thiazolidinediones/

8. ((peroxisome proliferator-activated receptor gamma or PPAR gamma or PPAR-gamma or PPARgamma or PPARG or NR1C3) adj5 (agonist$ or modulator$ or stimulat$ or stimulant$ or activat$)).tw.

9. (thiazolidinedione$ or glitazone$ or pioglitazone or rosiglitazone or troglitazone or netoglitazone or rivoglitazone or ciglitazone or balaglitazone or darglitazone or edaglitazone or e nglitazone or lobeglitazone).tw,nm.

10. 5 or 6 or 7 or 8 or 9

11. Randomised Controlled Trials as Topic/

12. random allocation/

13. Controlled Clinical Trials as Topic/

14. control groups/

15. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

16. double-blind method/

17. single-blind method/

18. Placebo/

19. placebo effect/

20. Drug Evaluation/

21. Research Design/

22. randomised controlled trial.pt.

23. controlled clinical trial.pt.

24. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

25. random$.tw.

26. (controlled adj5 (trial$ or stud$)).tw.

27. (clinical$ adj5 trial$).tw.

28. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

29. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

30. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

31. placebo$.tw.

32. controls.tw.

33. (RCT or RCTs).tw. or trial.ti.

34. or/11-33

35. 4 and 10 and 34

36. exp animals/ not humans.sh.

37. 35 not 36

Ovid search syntax

.pt. denotes a Publication Type term;

.ab. denotes a word in the abstract;

.fs. denotes a ‘floating’ subheading;

.sh. denotes a Medical Subject Heading (MeSH) term;

.ti. denotes a word in the title;

The ‘adj6’ operator indicates within 6 words;

.mp. indicates a search of title, original title, abstract, name of substance word and subject heading word;

‘$’ the dollar sign ($) stands for any character(s) indicates truncation;

tw. text word.

2.1.3 EMBASE search strategy

1. Bone fracture$.tw. or bone$.tw. or fracture$.tw. or fracture risk$.tw.
2. fracture$.tw.
3. Fractures$.tw., bone$.tw.
4. 1 or 2 or 3
5. PPAR gamma/ag, de, me, pd, tu
6. Peroxisome Proliferator-Activated Receptors/ag, de, me, pd, tu or Transcription Factors/ag, de, me, pd, tu
7. Thiazolidinediones/
8. ((peroxisome proliferator-activated receptor gamma or PPAR gamma or PPAR-gamma or PPARgamma or PPARG or NR1C3) adj5 (agonist$ or modulator$ or stimulat$ or stimulant$ or activat$)).tw.
9. (thiazolidinedione$ or glitazone$ or pioglitazone or rosiglitazone or troglitazone or netoglitazone or rivoglitazone or ciglitazone or balaglitazone or darglitazone or edaglitazone or e nglitazone or lobeglitazone).tw,nm.
10. 5 or 6 or 7 or 8 or 9
11. Randomised Controlled Trials as Topic/
12. random allocation/
13. Controlled Clinical Trials as Topic/
14. control groups/
15. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
16. double-blind method/
17. single-blind method/
18. Placebo/
19. placebo effect/
20. Drug Evaluation/
21. Research Design/
22. randomised controlled trial.pt.
23. controlled clinical trial.pt.
24. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
25. random$.tw.
26. (controlled adj5 (trial$ or stud$)).tw.
27. (clinical$ adj5 trial$).tw.
28. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

29. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

30. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

31. placebo$.tw.

32. controls.tw.

33. (RCT or RCTs).tw. or trial.ti.

34. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35. 4 and 10 and 34

36. exp animals/ not humans.sh.

37. 35 not 36

2.1.4 PubMed search strategy

#1 (Bone fracture* or bone* or fracture* or fracture risk*):[tiab]

#2 (fracture*):[tiab]

#3 (Fracture* or bone*):[tiab]

#4 (#1 or #2 or #3)

#5 [mh ^"PPAR gamma"/AG,DE,ME,PD,TU]

#6 [mh ^"Peroxisome Proliferator-Activated Receptors"/AG,DE,ME,PD,TU] or [mh ^"Transcription Factors"/AG,DE,ME,PD,TU]

#7 [mh ^Thiazolidinediones]

#8 (("peroxisome proliferator-activated receptor gamma" or "PPAR gamma" or "PPAR gamma" or "PPARgamma" or PPARG or NR1C3) near/5 (agonist* or modulator* or stimulat* or stimulant* or activat*)):[tiab]

#9 (thiazolidinedione* or glitazone* or pioglitazone or rosiglitazone or troglitazone or netoglitazone or rivoglitazone or ciglitazone or balaglitazone or darglitazone or edaglitazone or englitazone or lobeglitazone):[tiab]

#10 (#5 or #6 or #7 or #8 or #9)

#11 randomized controlled trial [pt]

#12 controlled clinical trial [pt]

#13 randomized [tiab]

#14 placebo [tiab]

#15 clinical trials as topic [mesh: noexp]

#16 randomly [tiab]

#17 drug therapy [sh]

#18 randomly [tiab]

#19 trial [tiab]

#20 groups [tiab]

#21 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 animals [mh] NOT humans [mh]

#23 #21 NOT #22

#24 #4 AND #10 AND #23

PubMed search syntax

[pt] denotes a Publication Type term;

[tiab] denotes a word in the title or abstract;

[sh] denotes a subheading;

[mh] denotes a Medical Subject Heading (MeSH) term (‘exploded’);

[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not ‘exploded’);

[ti] denotes a word in the title.

2.1.5 Web of Science search strategy

Thiazolidinediones AND bone fracture.

Articles identified through Cochrane Library **25**, MEDLINE **132**, EMBASE **291**, PubMed **284**, Web of Science **68** and **50** publications through Grey Literature.

2.2 Excluded studies

Supplemental Table 2-1. Excluded studies

Study	Reasons of exclusion	Population	TZDs mean age‡	Study design and country	Treatment groups	TZDs Dosage‡	Duration (Months)
NCT00951379; 2016	Pioglitazone as a rescue drug	Oral premalignant lesions (*n*=52)	59.9	Phase IIb, double-blind, RCTs, in Italy, Canada and USA	Pioglitazone vs. placebo	15-45 mg/d	6
Dormandy 2005	*Post-hoc* PROactive trial	T2DM with MVD (*n*=5238)	61.9	Prospective, double-blind RCT in 19 European countries	Pioglitazone vs. placebo	15-45 mg/d	34.5
DeFronzo 2011	*Post-hoc* ACT NOW trial	IGT (*n*=602)	52.3	Prospective, double-blind RCT in USA	Pioglitazone vs. placebo	30-45 mg/d	33.6
Scheen 2009	*Post-hoc* PROactive 17 trial	T2DM with MVD (*n*=1314)	61.7	Prospective, double-blind RCT in Europe	Pioglitazone vs. placebo	15-45 mg/d	34.5
Scheen 2009	*Post-hoc* PROactive18 trial	T2DM with MVD (*n*=1515)	62	Prospective, double-blind RCT in Europe	Pioglitazone vs. placebo	15-45 mg/d	34.5
Zinman 2010	*Post-hoc* ADOPT trial	T2DM (*n*=4351)	56.3	Double-blind RCTs in Europe and USA	Rosiglitazone vs. metformin/glyburide	4-8 mg/d	12
Kahn 2006	*Post-hoc* ADOPT trial	T2DM (*n*=4351)	56.3	Double-blind RCTs in Europe and USA	Rosiglitazone vs. metformin/glyburide	4-8 mg/d	60
BARI2D study 2009	*Post-hoc* ACCORD trial	T2DM with CAD (*n*=2160)	62.3	Double-blind RCTs in USA, in 5 countries	Insulin-sensitization vs. insulin-provision	NR	60
NCT00000620; 2016	Pioglitazone as a rescue drug	T2DM with CVD (*n*=10251)	62.2	Phase III, open-label randomized, factorial assignment	AHGs vs. no-AHGs	NR	59
Leiter 2014 NCT01098539	Terminated due to slow accrual	T2DM with CKD (*n*=495)	63.3	Phase III, double-blind, RCTs	TZDs + metformin + sulfonylurea + albiglutide + sitagliptin vs. no-TZDs	NR	13
Vaccaro 2017 NCT00700856	Terminated early due to the basis of a fatality analysis adjudicated cardiovascular event with a substantial percentage of patients not taking pioglitazone because of emerged concerns that possibly linked to bladder cancer.	T2DM (n=3,028)	62.4	Unblinded RCT, PROBE design in 57 diabetes clinics in Italy, TOSCA.IT trial	Pioglitazone + metformin vs. glimepiride + metformin	15-45 mg/day	57.3
DeFronzo 2013 NCT00121667	Pioglitazone as a rescue drug	T2DM (*n*=743)	54.6	Phase III, double-blind RCTs	Pioglitazone + metformin + saxagliptin + placebo vs. no-pioglitazone	15-45 mg/d	42
Jadzinsky 2009 Pfützner 2011 NCT00327015	Pioglitazone as a rescue drug	T2DM (*n*=1306)	51.9	Phase III, double-blind RCTs	Pioglitazone + metformin + saxagliptin¶ vs. no-pioglitazone	15-45 mg/d	12
NCT00680745; 2013	Pioglitazone as a rescue drug	T2DM (*n*=592)	59.8	Phase III, double-blind RCTs	Pioglitazone + dapagliflozin + glimepiride + placebo vs. no-pioglitazone		6

Abbreviations: *AHG;* anti-hyperglycaemic drugs, *CVD;* cardiovascular disease, *CAD;* coronary artery disease, *mg/d;* milligram pear day, NR*;* not report, *PROBE;* prospective randomized open, blinded end-point, *RCT*; randomised controlled trial, *T2DM;* type 2 diabetes mellitus, *TZD;* thiazolidinedione.

Notes: ‡Mean and dosages present for active TZDs drugs (pioglitazone or rosiglitazone or rivoglitazone), ¶Novel treatment of fixed-dose combination of 2 different classes of AHG.

2.3 Categorisation of the anti-hyperglycaemic therapies

Supplemental Table 2-2. Categorisation of the anti-hyperglycaemic therapies

Anti-hyper glycaemic agents (Generic Name)	Anti-hyper glycaemic agents (Trade Name)	Mechanism of action
TZDs class:		
Pioglitazone	Actos	TZDs: activating PPARs.
Rosiglitazone	Avandia	Stimulates the nuclear receptor PPAR-γ and to a lesser extent PPAR-α. It modulates genes transcription involved in control of glucose and lipid metabolism in muscle, adipose tissue, liver.
Rivoglitazone	-	
Pioglitazone/metformin	Actoplus Met, Piomet or	
Pioglitazone/alogliptin¶	Incresync or Oseni	Selective ligand of PPARγ and has no PPARα-binding action.
Pioglitazone/linagliptin¶	Janacti	Dual peroxisome proliferator-activated receptor α/γ agonist
Pioglitazone/sitagliptin¶	Politor	
Rosiglitazone/metformin¶	Avandment	
Aleglitazar	-	
Biguanide class:		
Metformin	Glucophage	Metformin: improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Metformin/glibenclamide¶	-	
Metformin/gliclazide¶	-	
Metformin/saxagliptin¶	Kombiglyze XR	
Metformin/sitagliptin¶	Janumet	
Sulfonylurea class:		Sulfonylureas bind to an ATP-sensitive K^+(KATP) channel on the cell membrane of pancreatic β cells. This inhibits a tonic, hyperpolarizing efflux of K^+, causing the electric potential over the membrane to become more positive. This depolarization opens voltage gated Ca^{2+} channels. The rise in intracellular Ca^{2+} leads to increased fusion of insulin granulae with the cell membrane and therefore increased secretion of (pro) insulin.
Glibenclamide	Glyburide	
Gliclazide	Diamicron	
Glimepiride	Amaryl	
Glipizide	Glucotrol	
Glinides	Meglitinides	
DPP4-Is class:		
Alogliptin	Nesina or Vipidia	Glucagon increases blood glucose levels and DPP4-Is reduce glucagon and blood glucose levels. The mechanism of DPP4-Is is to increase incretin levels (GLP1-RAs), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying and decreases blood glucose levels.
Linagliptin	BI-1356 or Tradjenta	
Omarigliptin	MK-3102	
Saxagliptin	BMS-477118 or Onglyza	
Sitagliptin	MK-0431 or Januvia	
Teneligliptin	Tenelia	
GLP1-RAs class:		GLP1-RAs is a potent antihyperglycemic hormone, inducing the β-cells of the pancreas to release the hormone insulin in response to rising glucose, while suppressing glucagon secretion.
Albiglutide	Eperzan and Tanzeum	
Dulaglutide	LY2189265	
Exenatide	Byetta or Bydureon	
Liraglutide	NN2211	
SGLT2-Is class:		SGLT2-Is is called gliflozins and lead to a reduction in blood glucose levels. Therefore, SGLT2 inhibitors have potential use in the treatment of T2DM. As studied on canagliflozin, a member of this class of drugs, gliflozins enhance glycemic control as well as reduce body weight and systolic and diastolic blood pressure.
Canagliflozin	Invokana or Sulisent	
Dapagliflozin	Farxiga or Forxiga	
Empagliflozin	Jardiance	
Insulin class:		
Insulin aspart	NovoLog/NovoRapid	Fast and short-acting
Insulin degludec	Tresiba	Ultralong-acting insulin
Insulin glargine	Lantus	Long-acting basal insulin
Insulin lispro	Humalog	Fast and short-acting

Abbreviations: *DPP4-Is;* dipeptidyl peptidase-4 inhibitor, *F;* female, *GLP1-RAs;* glucagon-like peptide-1 receptor agonist, *M;* male, *SGLT-2;* sodium glucose co-transporter-2 inhibitor, *NR;* not report, *SAEs; serious* adverse events; *PPARs;* peroxisome proliferator-activated receptors.
Note: ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG.

2.4 Risk of bias outcomes

Supplemental Figure 2-1. Risk of bias outcomes in individuals' studies included in the review

2.5 Studies characteristics outcomes

Supplemental Table 2-3. Baseline characteristics of TZDs therapies included trials

Study Trial registry	Population Sample size	T2DM† duration (years)	HbA1c† levels %	Prior stroke/TIA (%)	Prior fracture/ bone disease %	Mean age (years)‡ Males (%)	Study design and country	Parallel arms	Intervention vs. placebo or control	Background AHGs therapy	Intervention of interest dosage‡ mg/day (TZDs therapy)	Duration (weeks)
Intervention of interest (TZDs therapy) vs. placebo or control												
Kernan and Viscoli 2016 [141] NCT00091949	IR with stroke/TIA (*n*=3876)	IR	IR	100%	NR	63.5/63.5 66.7/64.3	Double-blind, RCT in 179 centres in 7 countries, IRIS trial	2	Pioglitazone vs. placebo	None	15, 30, 45	251**
Simuni 2015 [346] NCT01280123	Parkinson's disease (*n*=210)	IR	IR	NR	NR	61.3/59.0 72.0/68.0	Phase II, double-blind RCT in 35 centres in USA, NINDS Exploratory trial	3	Pioglitazone vs. placebo	None	15, 30, 45	44
Grey 2014 [351]	T2DM or IGT (*n*=86)	NR	7.4±3.5/7.5±3.2	NR	Fracture 5.0/5.0	64.0/63.0 49.0/53.0	Double-blind RCT in Australia	2	Pioglitazone vs. placebo	AHG + insulin	15-30	52
Bray 2013 [352] NCT00220961	IGT (*n*=602)	IGT	5.0/5.0	NR	NR	50.7/48.1 58.0/57.8	Prospective, double-blind RCT in 8 centres in USA, ACT NOW trial	2	Pioglitazone vs. placebo	None	30-45	126
Bone 2013 [350] NCT00708175	Postmenopausal IGT (*n*=156)	IGT	IGT	NR	Fracture 6.4/3.8	59.0/60.2	Prospective, double-blind RCT in 25 centres in USA	2	Pioglitazone vs. placebo	None	30-45	78
Marder 2013 [347] NCT00554853	Rheumatoid arthritis (*n*=256)	IR	IR	NR	NR	54.9**/54.9** 24.0/24.0	Double-blind, crossover RCT in USA	2	Pioglitazone vs. placebo	None	30-45	32
Sanyal 2010 [341] NCT00063622	Non-alcoholic steatohepatitis (*n*=163)	IR	IR	NR	NR	47.0/45.4 41.0/42.0	Phase III, double-blind RCT in USA, PIVENS trial	2	Pioglitazone vs. placebo	None	30	96
Ramachandran 2009 [470] NCT00276497	IGT (*n*=407)	IGT	5.8±0.4/5.8±0.4	NR	NR	45.1/45.5	Prospective, double-blind RCT in Asia and India, IDPP-2 trial	2	Pioglitazone vs. placebo	None	30	157
Aithal 2008 [471] N0192119052	Non-alcoholic steatohepatitis (*n*=74)	IR	5.8±0.6/5.9±1.0	NR	NR	52.0/55.0 70.0/51.0	Double-blind RCT in UK	2	Pioglitazone vs. placebo	None	30	52
Dormandy 2005 [140] NCT00174993	T2DM with macrovascular disease (*n*=5238)	8.0/8.0	NR	Stroke *n*=985 (18.8% vs. 18.8%) TIA *n*=299 (5.7% vs. 5.7%)	NR	61.9/61.6 67.0/66.0	Prospective, double-blind RCT in 19 European countries, PROactive trial	2	Pioglitazone vs. placebo	Metformin ± sulfonylurea ± insulin	15, 30, 45	150
Home 2014 [472] NCT00839527	T2DM (*n*=663)	9.2±6.1/8.5±6.3 /9.3±6.1	8.3±0.8/8.2±0.9/8. 3±0.9	NR	NR	55.1/55.7 52.0/61.0	Phase III, double-blind RCT in 234 centres in 9 countries HARMONY 5	3	Pioglitazone + albiglutide vs. placebo	Metformin + glimepiride	30-45	156
Chou 2012 [345] NCT00484198	T2DM (*n*=1886)	4.4±4.9/4.6±4.8 /4.9±6.1	7.7±0.5/7.7±0.5/7. 7±0.5	NR	NR	55.0/55.1/55.4 53.0/50.0/49.0	Phase III, double-blind RCT in 254 centres in 4 countries	4	Pioglitazone + rivoglitazone vs. placebo	Metformin ± sulfonylurea ± α-glucosidase Is ± meglitinide	Pioglitazone 45 Rivoglitazone 1-1.5	26
Truitt 2010 [473] NCT00143520	T2DM (*n*=438)	6.6±7.5/6±6.4/6 .7±5.6	7.9±0.8/8.1±0.9/8. 2±0.9	NR	NR	56.6/56.4/55.3 58.2/53.9/51.1	Double-blind RCT in USA	5	Pioglitazone + rivoglitazone vs. placebo	Metformin ± sulfonylurea	Pioglitazone 45 Rivoglitazone 1-3	26
NCT00722371; 2015 [474]	T2DM (*n*=1615)	NR	NR	NR	NR	58.9/58.9 56.0/59.0	Phase III double-blind RCT, factorial study in USA 0431-102-AM2 trial	7	Pioglitazone + sitagliptin¶ vs. sitagliptin + placebo	Metformin + sulfonylurea	15, 30, 45	54
NCT00511108; 2015 [475]	T2DM (*n*=211)	NR	7.9±0.9/7.7±0.8/8. 0±1.1	NR	NR	53.3/54.6/53.3 54.0/54.0/60.0	Phase I, double-blind RCT in USA, 0431-061 trial	4	Pioglitazone + sitagliptin¶ vs. sitagliptin + placebo	None	30	24
Kaku 2009 [344] UMIN000001363	T2DM with CVD (*n*=587)	≥5.0/≥5.0	7.6/7.5	Stroke 5.3% vs. 5.3%	NR	58.1/57.9 63.0/62.0	Prospective, open-label (PROBE) in Japan	2	Pioglitazone vs. control	Sulfonylurea ± biguanide ± α-glucosidase Is ± insulin	15, 30, 45	192

Abe 2010 [476]	T2DM with CKD on dialysis (*n*=63)	16.6±5.5/16.3±5.5	NR	NR	NR	65.2/67.2 68.0/68.0	Prospective, open-label RCT in Japan	2	Pioglitazone/conventional AHGs vs. control (AHGs excluding TZDs)	α-glycoside Is + mitiglinide	15-30	104
Yan 2015 [477] NCT00633282	T2DM/IGT with non-alcoholic liver disease (*n*=100)	NR	6.4±0.6/6.1±0.6	NR	NR	53.5/50.6	Open-label RCT in China	2	Pioglitazone vs. no-TZDs (lifestyle intervention + berberine)	None	15	16
Harrison 2012 [478]	IR with HCV (*n*=150)	IR	IR	NR	NR	52.0/51.0** 50.0/61.0	Open-label RCT in USA, SENSITIZE trial	2	Pioglitazone vs. no-TZDs (standard care of peginterferon α-2a + ribavirin)	None	30-45	88
Gold 2010 [343] NCT00428090	Alzheimer's disease (*n*=496)	IR	IR	NR	NR	71.7/72.5 36.0/40.0	Phase III, double-blind RCT, in 134 centres in 19 countries	3	Rosiglitazone vs. placebo	None	2-8	24
Gruntmanis 2010 [479]	T2DM with CVD (*n*=111)	NR	7.6±1.8/7.6±1.7	NR	NR	56.7/55.8 58.9/58.9	Prospective, double-blind RCT in USA	2	Rosiglitazone vs. placebo	NR AHG agents	4-8	24
GSK49653/334; 2008 [480] NCT00306644	T2DM and/or IR (*n*=555)	NR	NR	NR	NR	67.7/67.3 45.0/48.0	Phase IV, double-blind RCT in Sweden	2	Rosiglitazone vs. placebo	Metformin + sulfonylurea + nateglinide	4-8	52
GSK49635/351; 2008 [481] NCT00231387	T2DM with CVD or hypertension (*n*=60)	NR	NR	NR	NR	62.2/65.6 21.0/23.0	Phase IIIb, double-blind RCT in UK	2	Rosiglitazone vs. placebo	None ± metformin ± sulfonylurea	4-8	52
Zinman 2010 [340] NCT00116932	IGT (*n*=207)	IGT	IGT	NR	NR	50.0/55.0** 35.0/31.7	Double-blind RCT in Canada, CANOE trial	2	Rosiglitazone/metformin¶ vs. placebo	None	2/500-4/100	204
Bach 2013 [342] NCT00006305	T2DM with CAD (*n*=1360)	10.8±8.1/10.0±9.1	7.8±1.6/7.5±1.6	10% vs. 10%	NR	62.0/62.7 70.0/72.0	Randomised 2x2 factorial design study in 6 countries, BARI 2D trial	4	Rosiglitazone vs. no-TZDs	Metformin + sulfonylurea + insulin + meglitinide	NR	235
Erdmann 2015 [482] NCT01042769	T2DM or IR with CVD (*n*=1996)	NR	8.5/>10	NR	NR	Pre-DM 66.7/66.6 T2DM 65.8/65.8	Phase III, double-blind RCT in 812 centres in USA, ALEPREVENT trial	2	Aleglitazar vs. placebo	Sulfonylurea ± DPP4-Is ± GLP1-RAs ± biguanide	0.15	235
Esposito 2011 [483]	T2DM (*n*=110)	NR	8.0±1.0/8.1±1.0	NR	NR	54.2/54.2	Prospective, double-blind RCT in Italy	2	Pioglitazone vs. metformin	None	15, 30, 45	24
Seufert (b) 2008 [484] [485]	T2DM (*n*=639)	7±5.6/7.1±5.6	8.8±0.9/8.8±0.7	NR	NR	60.0/60.0	Double-blind, RCT in 3 countries	2	Pioglitazone vs. metformin	Sulfonylurea	15, 30, 45	52
Perez 2009 [486] NCT00727857	T2DM (*n*=600)	NR	8.9±0.1/8.6±0.1	NR	NR	54.7/53.7 41.0/47.0	Phase IIIb double-blind RCT in 6 countries	3	Pioglitazone/ metformin¶ vs. metformin	None	30	24
Wainstein 2012 [487] NCT00532935	T2DM (*n*=517)	3.3±3.5/3.2±4.0	8.9±1.3/ 9.0±1.3	NR	NR	52.2/52.4 52.0/55.0	Phase III, double-blind RCT in USA, 0431A-066	2	Pioglitazone vs. metformin/sitagliptin¶	Insulin	30-45	32
Bilezikian 2013 [348] NCT00679939	T2DM Postmenopausal (*n*=226)	3.9/3.3	6.8±0.7/6.8±0.7	NR	No osteoporosis	63.6/76.9	Double-blind RCT in Canada and USA	2	Rosiglitazone vs. metformin	Metformin + sulfonylurea	8	76
Borges 2011 [349] NCT00386100	T2DM (*n*=678)	2.3±3.1/2.6±3.3	8.6±0.9/8.6±0.9	NR	Fractures 15.0/15.0 Bone disease <1/<1	51.5/50.7 53.0/53.0	Phase IV, double-blind RCT in 98 centres in 9 countries	2	Rosiglitazone/metformin¶ vs. metformin	None	4-8	80
WH 2015 [488] NCT01217073	T2DM (*n*=1169)	5.3±4.4/5.8±4.6	8.1±0.9//8.1±0.9	NR	NR	55.9/55.9 56.0/57.0	Phase IIb, double-blind RCT in USA, MK-3102-006 trial	8	Pioglitazone/metformin vs. omarigliptin + placebo	Metformin	15-30	78
Tolman 2009 [489] NCT00494312	T2DM (*n*=2097)	5.8/5.6	9.5±2/9.5±2	NR	NR	54.0/55.0** 57.2/55.5	Double-blind RCT in 171 centres in USA	2	Pioglitazone vs. glyburide	Metformin ± sulfonylurea	15, 30, 45	144
Jain 2006 [490]	T2DM (*n*=502)	9.6±13.7/9.4±15.1	9.2±1.2/9.2±1.2	NR	NR	52.1/52.1 53.0/56.0	Prospective, double-blind RCT in 65 centres in Puerto Rico or USA	2	Pioglitazone vs. glyburide	None	15, 30, 45	56
Nissen 2008 [146] NCT00225277	T2DM with CHD (*n*=543)	5.8/5.9	NR	NR	NR	60.0/59.7 68.9/65.9	Prospective, double-blind RCT in 97 centres in USA, PERISCOPE trial	2	Pioglitazone vs. glimepiride	None + metformin + sulfonylurea	15, 30, 45	78
Umpierrez 2006 [491]	T2DM (*n*=203)	5.9±6.1/3.8±4.9	8.3±0.7/8.4±0.7	NR	NR	55.7/51.6 56.0/53.0	Open-label RCT in USA	2	Pioglitazone vs. glimepiride	Metformin	30-45	28
Seufert (a) 2008 [484] [492]	T2DM (*n*=630)	5.8±5.1/5.5±5.1	8.7±1/8.5±0.8	NR	NR	56.0/57.0 50.0/49.0	Double-blind, RCT in 75 centres in 3 countries	2	Pioglitazone vs. gliclazide	Metformin	15, 30, 45	52

Comaschi 2007 [493]	T2DM (*n*=420)	NR	8.5± 0.8/8.6± 0.9	NR	NR	59.1/59.1	Open-label RCT in Italy	2	Pioglitazone + sulfonylurea vs. metformin/glibenclamide¶	Metformin	15-30	24
Home 2009 [125] NCT00379769	T2DM (*n*=4447)	6.1/6.3/7.9/7.9	7.8/7.8/8/8	Stroke 2.3/1.8 vs. 2.6/2.9 TIA 2.4/2.3 vs. 2.2/2	NR	57/57.2 vs. 59.8/59.7 53.8/52.9 vs. 49/50.6	Prospective, open-label RCT in 327 centres in Europe and Australasia, RECORD trial	4	Rosiglitazone vs. metformin or sulfonylurea	Metformin + sulfonylurea	4-8	261
Kahn 2008 [159] NCT00279045	T2DM (*n*=4351)	3.2/3.9/3.6	7.3/7.3/7.3	NR	NR	56.3/56.8/56.5 55.7/59.4/58	Double-blind RCT in 490 centres in 3 countries, ADOPT trial	3	Rosiglitazone vs. metformin + glyburide	None	4-8	209
NCT00367055; 2010 [494]	T2DM (*n*=84)	NR	7.5±0.5/7.3±0.5	NR	NR	58.3/58.1 75.0/61.0	Phase IV, open-label RCT in France	2	Rosiglitazone + metformin¶ vs. gliclazide + metformin¶	Metformin	4-8	144
AVM100264; 2008 [495] NCT00359112	T2DM or IR (*n*=595)	NR	8.0±0.8/7.9±0.9	NR	NR	58.5/59.3 53.0/53.0	Phase IV, double-blind RCT in 18 centres in 11 countries	2	Rosiglitazone + metformin¶ vs. metformin + sulfonylurea	Metformin	4-8	52
DeFronzo 2012 [496] NCT00328627	T2DM (*n*=1554)	7.6±7.1/5.9±10. 5/6.0±5.0	8.5±0.7/8.6±0.7/8. 5±0.6	NR	NR	54.4/53.2/55.2 45.0/46.0/47.0	Double-blind RCT in 327 centres in 20 countries	5	Pioglitazone + alogliptin¶ vs. alogliptin + placebo	Metformin	15, 30, 45	26
Rosenstock 2010 [497] NCT00395512	T2DM (*n*=654)	3.2±3.5/3.2±3.7	8.7±0.9/8.8±0.9	NR	NR	53.0/53.0	Double-blind RCT in USA	4	Pioglitazone + alogliptin¶ vs. alogliptin	None	30	26
Gomis 2012 [498] NCT00736099	T2DM (*n*=2121)	≤1 and >5/ ≤1 and >5	7.8±1.0/7.3±0.9	NR	NR	57.8/57.8 53.0/52.0	Phase III, open-label trial in 232 centres in 31 countries	2	Pioglitazone/linagliptine¶ vs. linagliptine	Metformin + sulfonylurea	30	78
NCT01204294; 2014 [499]	T2DM (*n*=574)	NR	NR	NR	NR	60.4/60.8 79.0/69.0	Phase III, open-label RCT in 43 centres in Japan	7	TZDs + linagliptin vs. linagliptin	Metformin + sulfonylurea + biguanide + glinide + α-glycoside Is	NR	52
Takihata 2013 [500] UMIN000004716	T2DM (*n*=115)	NR	7.4±0.6/7.4±0.6	NR	NR	60.7/60.3 56.0/62.0	Open-label RCT in 9 centres in Japan COMPASS trial	2	Pioglitazone vs. sitagliptin	Metformin + sulfonylurea	15-30	24
NCT01777282; 2016 [501]	T2DM (*n*=374)	NR	NR	NR	NR	59.0/57.0 82.0/68.0	Phase III, open-label RCT in 49 centres in Japan	5	TZDs + albiglutide vs. albiglutide	Sulfonylurea + biguanide + glinide + α-glycoside Is	NR	52
NCT01468181; 2015 [502]	T2DM (*n*=394)	NR	NR	NR	NR	56.4/57.1 79.0/75.0	Phase III, open-label trial in Japan	5	TZDs + dulaglutide vs. dulaglutide	Sulfonylurea + biguanide + glinide + α-glycoside Is	NR	52
Araki 2015 [503] NCT01368081	T2DM (*n*=1160)	40±29/40±29	7.9±4.2/7.9±4.2	NR	NR	60.4/60.0 79.0/70.0	Phase III, double-blind RCT in 86 centres in Japan	13	TZDs + empagliflozin vs. empagliflozin	Metformin + sulfonylurea + biguanide + glinide + α-glycoside Is + DPP4-Is	NR	52
Abdul-Ghani 2014 [504] NCT01107717	T2DM (*n*=170)	5.1±0.6/5.1±0.7	8.6±0.2/8.6±0.2	NR	NR	46.0/47.0 62.0/55.0	Open-label RCT in San Antonio USA, EDICT trial	2	Pioglitazone/metformin/ exenatide vs. metformin/ sulfonylurea/insulin	None	15, 30, 45	104
Ruilope 2014 [505] NCT01043029†	T2DM with CKD-III (*n*=301)	10.2/9.6	7.6±0.9/7.5±0.9	NR	NR	68.2/66.8 47.0/50.0	Phase IIb, double-blind RCT in 4 countries, AleNephro trial	2	Pioglitazone + aleglitazar vs. no-pioglitazone	None ± metformin ± sulfonylurea	Pioglitazone 45 Aleglitazar 0.15	52
Bosi 2011 [506] NCT00432276†	T2DM (*n*=803)	7.5/6.9	8.3/8.1	NR	NR	54.3/55.9 52.0/51.1	Double-blind RCT in 22 countries	2	Pioglitazone + alogliptin vs. no-pioglitazone	Metformin + pioglitazone	30-45	52
Yoon 2011 [507] NCT00397631†	T2DM (*n*=520)	2.4±4.1/2.4±4.1	9.5±1.2/9.5±1.2	NR	NR	50.9/50.9 54.0/54.0	Phase III double-blind RCT in USA, 0431-064 trial	2	Pioglitazone + sitagliptin¶ vs. no-pioglitazone	None	30	24
Kashiwagi 2011 [508] NCT00372060†	T2DM (*n*=134)	NR	7.7±0.9/7.6±0.8	NR	NR	57.8/59.0 58.0/72.0	Phase III, double-blind RCT in Japan 0431-055	2	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	Pioglitazone	15	52
NCT01076075†; 2016 [509]	T2DM (*n*=422)	NR	8.4±0.9/8.4±0.8	NR	NR	54.9/54.4 46.0/45.0	Phase III, double-blind RCT in 3 countries, MK-0431-229 trial	2	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	Metformin + sulfonylurea + pioglitazone	30	54
Rosenstock 2006 [510] NCT00086502†	T2DM (*n*=353)	6.1±5.4/6.1±5.7	8.1±0.8/8.0±0.8	NR	NR	55.6/56.9 53.0/58.0	Phase III, double-blind RCT in USA	2	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	Pioglitazone	15, 30, 45	24

Fonseca 2013 [511] NCT00885352†	T2DM (*n*=313)	9.8±5.9/9.8±5.9	8.7±1.0/8.7±1.0	NR	NR	56.1/56.1 62.0/62.0	Phase III, double-blind RCT in 58 centres in 12 countries, MK-0431-128 trial	2	Pioglitazone + sitagliptin + placebo vs. no- pioglitazone	Metformin + pioglitazone ± sulfonylurea	30-45	26
Charbonnel 2006 [512] NCT00086515†	T2DM (*n*=701)	NR	8.0±0.8/8.0±0.8	NR	NR	54.5/54.5 57.0/57.0	Phase III, double-blind RCT in USA, 0431-020 trial	2	Pioglitazone + sitagliptin + glipizide + placebo vs. no-pioglitazone	Metformin + pioglitazone	15	24
Forst 2014 [513] NCT01106690†	T2DM (*n*=684)	10.5±7.0/10.5± 7.0	7.9±1.0/7.9±1.0	NR	NR	57.4/57.4 63.0/63.0	Phase III, double-blind RCT in 74 centres in 11 countries, CANTATA-MP trial	3	Pioglitazone + sitagliptine + canagliflozin + placebo vs. no-pioglitazone	Metformin + pioglitazone	30-45	26
Kovacs 2014 [514] NCT01289990†	T2DM (*n*=2705)	31±18.8/27±16. 1/26±15.8	8.1±0.9/8.1±0.9/8. 2±0.9	NR	NR	54.7/55.9/55.1/ 55.9 48/57/63/53	Phase III, double-blind trial in 69 centres in 8 countries	13	Pioglitazone + sitagliptin + empagliflozin + placebo vs. no-pioglitazone	Metformin + pioglitazone + sulfonylurea	30-45	76
Philis-Tsimikas 2013 [515] NCT01046110†	T2DM (*n*=454)	7.8±6.1/7.8±6.1	8.9±1.0/8.9±1.0	NR	NR	55.7/55.7 59.0/59.0	Phase III, open-label RCT in 78 centres in 7 countries, BEGIN™ trial	2	Pioglitazone + sitagliptin + insulin degludec vs. no-pioglitazone	Metformin+ pioglitazone + sulfonylureas + glinides	NR	26
Nauck 2016 [516] NCT01183013	T2DM (*n*=936)	≤1 and >10/≤1 and >10	8.1±0.9/8.1±0.9	NR	NR	57.1/57.1 54.0/54.0	Phase III, double-blind RCT in 132 centres in 6 countries	7	Pioglitazone + linagliptin¶ vs. no-pioglitazone	Pioglitazone	15, 30, 45	30
Gantz 2017 [517] NCT01697592†	T2DM (*n*=580)	9.18±5.4	7.9±0.6	NR	NR	61.0/60.5 72.0/72.0	Phase III, double-blind RCT in Japan MK-3102-015 trial	10	Pioglitazone/omarigliptin + placebo vs. no-pioglitazone	Pioglitazone + sulfonylurea + biguanide + glinide + α-glycoside Is	NR	52
Hollander 2011 [518] NCT00295633†	T2DM (*n*=565)	5.2±10.2/5.1±5. 4	8.3±1.1/8.2±1.1	NR	NR	54.9/54.0 51.0/46.0	Phase III, double-blind RCT in USA	3	TZDs + saxagliptin + placebo vs. no-TZDs	TZDs	Pioglitazone 30-45 Rosiglitazone 4-8	76
Kadowaki 2013 [519] NCT01026194†	T2DM (*n*=204)	7.3±5.3/8.1±5.8	8.1±0.8/7.9±0.8	NR	NR	60.4/60.4 71.0/71.0	Phase III, double-blind RCT in Japan	2	Pioglitazone/teneligliptin¶ + placebo vs. no-pioglitazone	Pioglitazone	NR	52
Davies 2015 [520] NCT01272232†	T2DM with metabolism and nutrition disorder (*n*=844)	7.3±5.4/7.3±5.4	7.9±0.8/7.9±0.8	NR	NR	54.9/54.9 50.0/50.0	Phase III, double-blind RCT in 126 centres in 9 countries SCALE™ trial	3	TZDs + liraglutide + placebo vs. no-TZDs	Metformin + TZDs + sulfonylurea	NR	68
Kiyosue 2018 [521] NCT01512108†	T2DM (*n*=360)	8.1±6.1	8.1±0.8/8.1±0.8	NR	NR	59.5/59.5 73.0/73.0	Phase III, open-label RCT in 36 centres in Japan	2	TZDs + liraglutide + additional AHG vs. no-TZDs	Metformin + TZDs + glinide + α-glycoside Is	NR	52
Norwood 2012 [522] NCT00753896†	T2DM (*n*=134)	6.0	7.2±0.9/7.2±0.9	NR	NR	55.0/55.0 55.0/55.0	Phase III, crossover open-label, randomised trial in 6 countries	2	TZDs + metformin + exenatide vs. no-TZDs	TZDs	Pioglitazone 30-45 Rosiglitazone ≥4	52
Wysham 2014 [523] NCT01064687†	T2DM (*n*=978)	8.7±5.6/8.7±5.6	8.1±1.3/8.1±1.3	NR	NR	55.7/55.7 58.0/58.0	Phase III, double-blind RCT in 89 centres in 4 countries, AWARD-1 trial	4	Pioglitazone+ exenatide + dulaglutide + placebo vs. no-pioglitazone	Metformin + pioglitazone	30	52
NCT00765817†; 2015 [524]	T2DM (*n*=259)	NR	NR	NR	NR	59.0/59.0 57.0/57.0	Phase III, double-blind RCT in 59 centres in 4 countries	2	Pioglitazone + exenatide + insulin glargine + placebo vs. no-pioglitazone	Metformin + pioglitazone	NR	30
Bode 2015 [525] NCT01106651†	T2DM (*n*=714)	11.7±7.5/11.7± 7.5	7.7±0.8/7.7±0.8	NR	NR	63.6/63.6 56.0/56.0	Phase III, double-blind RCT in 90 centres in 17 countries	3	TZDs + canagliflozin + placebo vs. no-TZDs	Metformin + sulfonylurea + TZDs + α-glycoside Is + DPP4-Is + insulin	NR	104
Rosenstock 2012 [526] NCT00683878†	T2DM (*n*=420)	5.6±5.9/5.0±5.0	8.3±0.9/8.3±1	NR	NR	53.8/53.5 48.7/51.0	Double-blind RCT in 105 centres in 8 countries	3	Pioglitazone + dapagliflozin + placebo vs. no-pioglitazone	Pioglitazone	30-45	24
Kovacs 2014 [514] NCT01210001†	T2DM (*n*=498)	>10.0/>10.0	8.1±0.8/8.2±0.9	NR	NR	54.5/54.6 50.5/44.2	Phase III, double-blind RCT in 69 centres in 8 countries, EMPA-REG PIO™ trial	3	Pioglitazone + empagliflozin + placebo vs. no-pioglitazone	Pioglitazone ± metformin	30-45	24
Garber 2012 [527] NCT00972283†	T2DM (*n*=1004)	13.5	8.4±0.9/8.3±0.8	NR	NR	58.1/95.2 54.0/54.0	Phase III, open-label RCT in 136 centres in 4 countries, BEGIN™ trial	2	± Pioglitazone + insulin degludec + insulin glargine vs. no-pioglitazone	Metformin + pioglitazone	NR	78
Fulcher 2019 [528] NCT01009580†	T2DM (*n*=446)	18.3±8.6	8.4±0.8/8.4±0.8	NR	NR	58.7/58.7 56.0/56.0	Phase III, open-label RCT in 53 centres in 3 countries, BOOST™ trial	2	± Pioglitazone + insulin degludec/insulin aspart + biphasic insulin aspart vs. no-pioglitazone	Metformin + pioglitazone + DPP4-Is	NR	27

Gross 2016 [529] NCT01175824	T2DM (*n*=476)	11.5±7.1	8.6±0.7	NR	NR	57.5/57.5 45.0/45.0	Phase IV, open-label RCT in 8 countries	2	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	Metformin + pioglitazone ± insulin	NR	24

Abbreviations: *AH*, anti-hyperglycaemic drugs; *BMD*, bone mineral density; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease; *CAD*, coronary artery disease; *CHD*, coronary heart disease, *DPP4-Is*, dipeptidyl peptidase-4 inhibitors; *GLP1-RAs*, glucagon-like peptide-1 receptor agonists; *HbA_{1c}*, glycosylated form of haemoglobin; *HCV*, hepatitis C virus; *IGT*, impaired glucose tolerance; *IR*, insulin resistance; *mg/d*, milligram pear day; NR, not report; *RCT*, randomised controlled trial; *T2DM*, type 2 diabetes mellitus; *TZD*, thiazolidinedione; *TIA*, transient ischemic attack.
Note: ‡ Mean age and dosages present for active TZDs drugs (pioglitazone or rosiglitazone or rivoglitazone or aleglitazar); ** Median age or follow-up; ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG; †these studies report fractures in both groups however all their participants had been exposed to TZDs.

2.6 Fractures results outcomes

Supplemental Table 2-4. Studies results of fractures adverse events

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs Non-stress Stress Low-energy High-energy Pathological Non-pathologic Low-energy, non-pathologic	133 F: 64 M: 64 204 10 F: 88 M: 90 F: 6 M: 29 3 F: 96 M: 119 F: 88 M: 88	1939 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293	94 F: 48 M: 44 137 8 F: 73 M: 46 F: 4 M: 18 3 F: 79 M: 62 F: 73 M: 4	1937 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 59 upper-limb (16 humerus, 20 radius, 7 ulna, 4 carpal, 12 metacarpal/phalange), 14 proximal-lower-limb (11 hip, 8 pelvis, 3 femur, 24 spine (7 lumbar, 12 thoracic, 5 cervical/sacrum)), 6 rib, 62 distal-lower-limb (1 patella, 23 fibula, 17 tibia, 4 tarsal, 17 metatarsal/phalange), 13 other (4 skull/face, 1 scapula, 0 clavicle) Pioglitazone M: 34 upper-limb (9 humerus, 10 radius, 1 ulna, 3 carpal, 11 metacarpal/phalange), 15 proximal-lower-limb (14 hip, 4 pelvis, 1 femur, 30 spine (17 lumbar, 10 thoracic, 3 cervical/sacrum)), 43 rib, 55 distal-lower-limb (2 patella, 14 fibula, 17 tibia, 5 tarsal, 17 metatarsal/phalange), 21 other (13 skull/face, 1 scapula, 3 clavicle) Placebo F: 34 upper-limb (7 humerus, 12 radius, 7 ulna, 2 carpal, 6 metacarpal/phalange), 14 proximal-lower-limb (10 hip, 7 pelvis, 4 femur, 24 spine (12 lumbar, 7 thoracic, 5 cervical/sacrum)), 12 rib, 33 distal-lower-limb (2 patella, 9 fibula, 7 tibia, 1 tarsal, 14 metatarsal/phalange), 11 other (2 skull/face, scapula, 2 clavicle) Placebo M: 34 upper-limb (10 humerus, 7 radius, 6 ulna, 2 carpal, 9 metacarpal/phalange), 7 proximal-lower-limb (7 hip, 3 pelvis, femur, 4 spine (2 lumbar, 2 thoracic, 0 cervical/sacrum)), 17 rib, 20 distal-lower-limb (patella, 6 fibula, 4 tibia, tarsal, 10 metatarsal/phalange), 15 other (9 skull/face, 0 scapula, 3 clavicle) Overall multiple fractures[§] 190 (94 F; 96 M) (128 (64F/64M pioglitazone) and (92 (48F/44M placebo)
Grey 2014 [351]	Pioglitazone vs. placebo	AEs	2	43	0	43	Pioglitazone: 2 ankle, 1 toe
Bray 2013 [352]	Pioglitazone vs. placebo	AEs	9	303	8	299	Pioglitazone: 9 traumatic fractures (0 hand, 1 right collarbone, 3 wrists, 1 tibia, 1 fibula, 2 foot, 0 ankle, 1 toe) Placebo: 8 traumatic fractures (1 hand, 0 right collarbone, 0 wrist, 0 tibia, 1 fibula, 2 foot, 3 ankle, 1 toe)
Bone 2013 [350]	Pioglitazone vs. placebo	AEs	F:1	F:78	F:3	F:78	Pioglitazone postmenopausal F (pathological fracture): radius, metacarpus Placebo postmenopausal F (pathological fracture): ankle, lateral malleolus, metatarsal
Sanyal 2010 [341]	Pioglitazone vs. placebo	AEs	3	80	5	83	Pioglitazone 30 mg: 3 Placebo: 5
Ramachandran 2009 [470]	Pioglitazone vs. placebo	AEs	4	204	4	203	Pioglitazone 30 mg: traumatic fracture (RTA) Placebo: traumatic fracture (RTA)
Aithal 2008 [471]	Pioglitazone vs. placebo	AEs	0	37	0	37	No fracture events
Dormandy 2005 [140]	Pioglitazone vs. placebo	AEs	74 F:44 M:30	2605 F:870 M:1735	60 F:23 M:37	2633 F:905 M:1728	Pioglitazone F: 6 spine, 2 hip, 7 proximal-limbs, 22 distal-limbs, 7 undefined limb, 2 osteoporotic/pathological Placebo F: 0 spine, 0 hip, 1 proximal-limb, 11 distal-limbs, 4 undefined limb, 2 osteoporotic/pathological M NR
Home 2014 [472] NCT00839527	Pioglitazone + albiglutide vs. placebo	AEs	1	548	5	115	Pioglitazone 30-45 mg + metformin ≥1500 mg + glimepiride 4 mg: 1/277 (AEs: rib) Albiglutide 30 mg + metformin ≥1500 mg + glimepiride 4 mg: 2/271 (AEs: rib) Metformin + glimepiride + placebo AEs: 3/115 (rib)
Truitt 2010 [473]	Pioglitazone + rivoglitazone vs. placebo	AEs	3	347	1	91	Pioglitazone 45 mg: 1/90 (traumatic multiple fracture (RTA) Rivoglitazone 1 mg: 1/86 (foot) Rivoglitazone 2 mg: 1/85 (foot) Rivoglitazone 3 mg: 0/86 Placebo: 1/91 (foot)
Kaku 2009 [344]	Pioglitazone vs. control	AEs	18	293	18	294	NR
Abe 2010 [476]	Pioglitazone/conventional AHG vs. control	AEs	0	31	0	32	No fracture events
Gold 2010 [343]	Rosiglitazone vs. placebo	AEs	2 F:2 M:0	331 129 71	3 F:3 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 2/166 (hip, hand) Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: hip, upper arm, wrist.
Gruntmanis 2010 [479]	Rosiglitazone vs. placebo	AEs	2 F:1 M:1	56 F:23 M:33	0 F:0 M:0	55 F:22 M:33	Rosiglitazone F: left humerus (fall) M: rib (fall)
GSK49653/334; 2008 [480]	Rosiglitazone vs. placebo	AEs	0	277	1	278	Placebo T2DM AEs: facial fracture
Zinman 2010 [340]	Rosiglitazone/metformin[¶] vs. placebo	AEs	4	103	6	104	NR
Bach 2013 [342]	Rosiglitazone vs. no-TZDs	Bone fracture	82 50	1084 680	74 45	1076 680	NR

			F:29 M:21	F:210 M:470	F:18 M:27	F:210 M:470	
Erdmann 2015 [482]	Aleglitazar vs. placebo	AEs	2	999	5	997	Aleglitazar 0.15 mg: 1 fracture in T2DM and other on pre-diabetic
Esposito 2011 [483]	Pioglitazone vs. metformin	AEs	0	55	0	55	No fracture events
Seufert J (b) 2008 [484] [485]	Pioglitazone vs. metformin	AEs	0 F:0 M:0	319 F:148 M:171	2 F:1 M:1	320 F:145 M:175	NR
Perez 2009 [486]	Pioglitazone/metformin¶ vs. metformin	AEs	1 F:1 M:0	390 F:234 M:156	1 F:0 M:1	210 F:112 M:98	Pioglitazone/metformin F: 1/200 wrist Pioglitazone: 0/190 Metformin M: 1/210 traumatic (RTA) wrist
Borges 2011 [349]	Rosiglitazone/metformin¶ vs. metformin	AEs	5 F:5 M:0	344 F:160 M:184	4 F:3 M:1	334 F:158 M:176	Rosiglitazone/metformin AEs: 5 Metformin AEs: 4
Tolman 2009 [489]	Pioglitazone vs. glibenclamide (glyburide)	AEs	30 F:16 M:14	1051 F:450 M:601	27 F:13 M:14	1046 F:465 M:581	NR
Nissen 2008 [146]	Pioglitazone vs. glimepiride	AEs	8 F:6 M:2	270 F:84 M:186	0 F:0 M:0	273 F:93 M:180	Pioglitazone: upper-limb, 2 lower-limb, hand, facial, 2 humerus, wrist, metacarpal, rib, malleolar, 2 foot NR by gender
Seufert J (a) 2008 [484] [492]	Pioglitazone vs. gliclazide	AEs	1 F:1 M:0	317 F:156 M:161	1 F:1 M:0	313 F:159 M:154	NR
Comaschi 2007 [493]	Pioglitazone + sulfonylurea vs. metformin/glibenclamide¶	AEs	1	340	0	80	Pioglitazone: 1/170 hip arthroplasty Pioglitazone + metformin: 0/103 Pioglitazone + sulfonylurea: 0/67 Metformin + glibenclamide: 0/80
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs	185 F:124 M:61	2220 F:1078 M:1142	118 F:68 M:50	2227 F:1075 M:1152	Rosiglitazone F: 8 spine, 7 femur/hip, 0 pelvis, 63 upper-limb, 47 distal-lower-limb, 11 other Rosiglitazone M: 6 spine, 3 femur/hip, 0 pelvis, 23 upper-limb, 23 distal-lower-limb, 14 other Active control F: 4 spine, 7 femur/hip, 1 pelvis, 36 upper-limb, 16 distal-lower-limb, 1 other Active control M: 5 spine, 1 femur/hip, 3 pelvis, 19 upper-limb, 11 distal-lower-limb, 15 other
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs High-energy or low-energy Pathological/osteoporotic	92 F:60 M:32 F: 7 M: 0 F: 10 M: 0	1456 F:645 M:811 F:645 M:811 F:645 M:811	108 F:51 M:57 F: 10 M: 0 F: 7 M: 0	2895 F:1195 M:1700 F:1195 M:1700 F:1195 M:1700	Rosiglitazone F: 1spine, 22 upper-limb (3 upper-limb, 0 forearm, 5 humerus, 1 radius, 8 hand, 5 wrist, 1 clavicle), 36 lower-limb (2 hip, 0 pelvic, 2 femur, 1 lower-limb, 1 tibia, 3 fibula, 5 ankle, 1 patella, 22 foot), 4 thoracic cage, 1 skull and facial, 0 not specific (60/645 total AEs) Rosiglitazone M: 3 spine, 10 upper-limb (0 upper-limb, 2 humerus, 1 radius, 6 hand, 2 wrist, 0 clavicle), 10 lower-limb (1 hip, 0 femur, 1 lower-limb, 2 tibia, 2 fibula, 2 ankle, 0 patella, 3 foot), 9 thoracic cage, 0 skull and facial, 2 not specific (32/811 total AEs) Metformin F: 1 spine, 10 upper-limb (2 upper-limb, 0 forearm, 0 humerus, 1 radius, 4 hand, 3 wrist, 0 clavicle), 18 lower-limb (2 hip, 2 pelvic, 0 femur, 2 lower-limb, 0 tibia, 2 fibula, 6 ankle, 1 patella, 7 foot), 2 thoracic cage, 0 skull and facial, 0 not specific (30/590 total AEs) Metformin M: 0 spine, 7 upper-limb (1 upper-limb, 0 humerus, 2 radius, 3 hand, 2 wrist, 1 clavicle), 13 lower-limb (0 hip, 2 femur, 0 lower-limb, 0 tibia, 1 fibula, 3 ankle, 0 patella, 8 foot), 8 thoracic cage, 1 skull and facial, 1 not specific (29/864 total AEs) Glyburide F: 1 spine, 9 upper-limb (1 upper-limb, 1 forearm, 0 humerus, 2 radius, 1 hand, 4 wrist, 0 clavicle), 8 lower-limb (0 hip, 0 pelvic, 0 femur, 0 lower-limb, 1 tibia, 0 fibula, 3 ankle, 0 patella, 4 foot), 1 thoracic cage, 1 skull and facial, 2 not specific (21/605 total AEs) Glyburide M: 1spine, 10 upper-limb (1 upper-limb, 3 humerus, 3 radius, 0 hand, 2 wrist, 2 clavicle), 16 lower-limb (1 hip, 0 femur, 0 lower-limb, 0 tibia, 0 fibula, 3 ankle, 1 patella, 11 foot), 2 thoracic cage, 1 skull and facial, 1 not specific (28/836 total AEs)
DeFronzo 2012 [496]	Pioglitazone + alogliptin¶ vs. alogliptin + placebo	AEs	0	1168	0	386	No fracture events Pioglitazone: 0/388 Pioglitazone + alogliptin: 0/780 Alogliptin: 0/257 Placebo: 0/129
Rosenstock 2010	Pioglitazone + alogliptin¶ vs. alogliptin	AEs	0	490	0	164	No fracture events Pioglitazone: 0/163 Pioglitazone + alogliptin: 0/327 Alogliptin: 0/164
NCT01468181; 2015 [502]	TZDs + dulaglutide vs. dulaglutide	AEs	2	66	5	328	TZDs + dulaglutide 0.75 mg AEs: 2/66 (fracture, foot) Dulaglutide 0.75 mg + sulfonylurea AEs: 4/131 (hand, foot, 2 tooth) Dulaglutide 0.75 mg + biguanide AEs: 0/61 Dulaglutide 0.75 mg + glinide SAEs: 0/71

							Dulaglutide 0.75 mg + α-glycoside Is AEs: 1/65 (radius)
Abdul-Ghani 2014 [504]	Pioglitazone/metformin/exenatide vs. metformin/sulfonylurea/insulin	AEs	0	79	0	91	No fracture events
Ruilope 2014† [505]	Pioglitazone + aleglitazar vs. no-pioglitazone	AEs	5	301	0	0	Pioglitazone 45 mg: 2/152 (clavicle, rib and scapula) Aleglitazar 0.15 mg: 3/149 (humerus, ankle, foot)
Bosi 2011† [506]	Pioglitazone + alogliptin vs. no-pioglitazone	AEs	10	803	0	0	Pioglitazone + metformin + alogliptin: 6/404 Pioglitazone + metformin: 4/399
Kovacs 2014† [514]	Pioglitazone + empagliflozin + placebo vs. no-pioglitazone	AEs	7	498	0	0	Empagliflozin 10 mg: 2/165 Empagliflozin 25 mg: 1/168 Placebo: 4/165
Hollander 2011† [518]	TZDs + saxagliptin + placebo vs. no-TZDs	AEs	6	565	0	0	TZDs + saxagliptin 2.5 mg: 4/195 TZDs + saxagliptin 5 mg: 1/186 TZDs + placebo: 1/184
Kadowaki 2013† [519]	Pioglitazone/teneligliptin¶ + placebo vs. no-pioglitazone	AEs	2	204	0	0	Pioglitazone + teneligliptin/teneligliptin: 2/103 thoracic vertebra fracture Pioglitazone + teneligliptin/placebo: 1/101 radius
Rosenstock 2012† [526]	Pioglitazone + dapagliflozin + placebo vs. no-pioglitazone	AEs	2 F:1 M:1	420 F:212 M:208	0 F:0 M:0	0 F:0 M:0	Pioglitazone + dapagliflozin: 2/281 limb fracture F: foot M: hand Pioglitazone + placebo: 0/139
Gross 2016† [529]	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	AEs	4	476	0	0	Insulin lispro: wrist, tooth/236 Insulin lispro + insulin glargine: lower-limb, tooth/240

Abbreviations: *AEs*, adverse events; *F*, female; *M*, male; *RTA*, road traffic accident; *TZD*, thiazolidinedione.
Note: ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG; §Multiple fractures per person; †these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-5. Studies results of fractures serious adverse events

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	Non-stress Stress SAEs Low-energy High-energy Pathological Non-pathologic Low-energy, non-pathologic Serious, low-energy, non-pathologic	204 10 F: 41 M: 58 F: 88 M: 90 F: 6 M: 29 3 F: 96 M: 119 F: 88 M: 88 F: 35 M: 41	 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293	137 8 F: 38 M: 24 F: 73 M: 46 F: 4 M: 18 3 F: 79 M: 62 F: 73 M: 45 F: 37 M: 15	 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 59 upper-limb (16 humerus, 20 radius, 7 ulna, 4 carpal, 12 metacarpal/phalange), 14 proximal-lower-limb (11 hip, 8 pelvis, 3 femur, 24 spine (7 lumbar, 12 thoracic, 5 cervical/sacrum)), 6 rib, 62 distal-lower-limb (1 patella, 23 fibula, 17 tibia, 4 tarsal, 17 metatarsal/phalange), 13 other (4 skull/face, 1 scapula, 0 clavicle) Pioglitazone M: 34 upper-limb (9 humerus, 10 radius, 1 ulna, 3 carpal, 11 metacarpal/phalange), 15 proximal-lower-limb (14 hip, 4 pelvis, 1 femur, 30 spine (17 lumbar, 10 thoracic, 3 cervical/sacrum)), 43 rib, 55 distal-lower-limb (2 patella, 14 fibula, 17 tibia, 5 tarsal, 17 metatarsal/phalange), 21 other (13 skull/face, 1 scapula, 3 clavicle) Placebo F: 34 upper-limb (7 humerus, 12 radius, 7 ulna, 2 carpal, 6 metacarpal/phalange), 14 proximal-lower-limb (10 hip, 7 pelvis, 4 femur, 24 spine (12 lumbar, 7 thoracic, 5 cervical/sacrum)), 12 rib, 33 distal-lower-limb (2 patella, 9 fibula, 7 tibia, 1 tarsal, 14 metatarsal/phalange), 11 other (2 skull/face, scapula, 2 clavicle) Placebo M: 34 upper-limb (10 humerus, 7 radius, 6 ulna, 2 carpal, 9 metacarpal/phalange), 7 proximal-lower-limb (7 hip, 3 pelvis, femur, 4 spine (2 lumbar, 2 thoracic, 0 cervical/sacrum)), 17 rib, 20 distal-lower-limb (patella, 6 fibula, 4 tibia, tarsal, 10 metatarsal/phalange), 15 other (9 skull/face, 0 scapula, 3 clavicle) Overall multiple fractures[§] 178 (77 F; 101 M) (99 (41F/58M pioglitazone) and (99 (38F/24M placebo)
Simuni 2015 [346]	Pioglitazone vs. placebo	SAEs	1	139	0	71	Pioglitazone 15 mg: 1/72 (ankle) Pioglitazone 45 mg: 0/67
Bone 2013 [350]	Pioglitazone vs. placebo	SAEs	F:0	F:78	F:1	F:78	Pioglitazone postmenopausal F: 0 Placebo postmenopausal F (pathological fracture): ankle
Marder 2013 [347]	Pioglitazone vs. placebo	SAEs	1	129	0	127	Pioglitazone: hip
Sanyal 2010 [341]	Pioglitazone vs. placebo	SAEs	0	80	2	83	Pioglitazone 30 mg: 0 Placebo SAEs: 2
Home 2014 [472] NCT00839527	Pioglitazone + albiglutide vs. placebo	SAEs	1	548	1	115	Pioglitazone 30-45 mg + metformin ≥1500 mg + glimepiride 4 mg: 1/277 (SAEs: ankle) Albiglutide 30 mg + metformin ≥1500 mg + glimepiride 4 mg: 1/271 (SAEs: thoracic vertebra fracture) Metformin + glimepiride + placebo SAEs: 0/115
Chou 2012 [345]	Pioglitazone + rivoglitazone vs. placebo	SAEs	1	1749	1	137	Pioglitazone 45 mg: 0/739 Rivoglitazone 1 mg: 0/269 Rivoglitazone 1.5 mg: 1/741 (spinal compression fracture) Placebo: 1/137 (hand)
NCT00722371; 2015 [474]	Pioglitazone + sitagliptin[¶] vs. sitagliptin + placebo	SAEs	3	1384	1	231	Pioglitazone: 1/693 foot Pioglitazone/sitagliptin: 2/691 (upper-limb, foot) Sitagliptin: 1/231 foot
NCT00511108; 2015 [475]	Pioglitazone + sitagliptin[¶] vs. sitagliptin + placebo	SAEs	1	106	0	105	Pioglitazone 30 mg + sitagliptin 100 mg: 1/52 (tibia) Pioglitazone 30 mg: 0/54 Sitagliptin 100 mg: 0/52 Placebo: 0/53
Yan 2015 [477]	Pioglitazone vs. no-TZDs	SAEs	0	47	0	53	No fracture events
Harrison 2012 [478]	Pioglitazone vs. no-TZDs	SAEs	1	77	0	73	Pioglitazone: lower-limb
Gold 2010 [343]	Rosiglitazone vs. placebo	SAEs	0 F:0 M:0	331 129 71	1 F:1 M:0	165 60 40	Rosiglitazone 2 mg F SAEs: 0/166 Rosiglitazone 2 mg SAEs: 0/165 Placebo F SAEs: hip
GSK49653/334; 2008 [480]	Rosiglitazone vs. placebo	SAEs	0	277	3	278	Placebo IR SAEs: femoral neck, upper-limb, radius
GSK49635/351; 2008 [481]	Rosiglitazone vs. placebo	SAEs	0	30	2	30	Placebo: pubic rami, humerus
Wainstein 2012 [487]	Pioglitazone vs. metformin/sitagliptin[¶]	SAEs	0	256	1	261	Pioglitazone: 0/256 Metformin/sitagliptin: 1/261 femur
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	SAEs	F:5	F:114	F:1	F:112	Rosiglitazone 8 mg postmenopausal F (pathological fractures): lumbar spine, wrist (fall), fingers (fall), lower leg (fall), toes (trauma) Metformin (pathological fractures): wrist (fall)
Borges 2011 [349]	Rosiglitazone/metformin[¶] vs. metformin	SAEs	2 F:2 M:0	344 F:160 M:184	0 F:0 M:0	334 F:158 M:176	Rosiglitazone/metformin: 0 Rosiglitazone/metformin F: 2 ankle Metformin: 0
WH 2015 [488]	Pioglitazone/metformin/placebo vs. omarigliptin + placebo	SAEs	1	80	0	1089	Metformin/placebo: 1/80 (rib) Omarigliptin 0.25 mg: 0/113

							Omarigliptin 1 mg: 0/115 Omarigliptin 3 mg: 0/114 Omarigliptin 10 mg: 0/115 Omarigliptin 25 mg: 0/114 Placebo: 0/113
Jain 2006 [490]	Pioglitazone vs. glyburide	SAEs	0	251	2	251	Glyburide: ankle
Umpierrez 2006 [491]	Pioglitazone vs. glimepiride	SAEs	1	107	1	96	Pioglitazone: Foot Glimepiride: Foot
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	SAEs	49	2220	36	2227	NR
NCT00367055; 2010 [494]	Rosiglitazone + metformin¶ vs. gliclazide + metformin¶	SAEs	0	43	1	41	Gliclazide + metformin: wrist
AVM100264; 2008 [495]	Rosiglitazone + metformin¶ vs. metformin + sulfonylurea	SAEs	2	294	1	301	Rosiglitazone + metformin: femur, humerus Metformin + sulfonylurea: femoral neck
Gomis 2012 [498]	Pioglitazone/linagliptine¶ vs. linagliptine	SAEs	2	589	13	1532	Pioglitazone 30 mg + linagliptine: 2foot Linagliptine: spinal compression, hip, femur, humerus, radius, ulna, hand, scapula, lower-limb, tibia, fibula, ankle, rib
NCT01204294; 2014 [499]	TZDs + linagliptin vs. linagliptin	SAEs	0	74	3	500	TZDs + linagliptin: 0/74 Sulfonylurea + metformin: 0/63 Sulfonylurea + linagliptin: 1/143 (ankle) Biguanide + linagliptin: 1/82 (lumbar vertebra fracture) Glinide + linagliptin: 1/66 (clavicle) α-glycoside Is + metformin: 0/61 α-glycoside Is + linagliptin: 0/85
Takihata 2013 [500]	Pioglitazone vs. sitagliptin	SAEs	0	57	0	58	No fracture events
NCT01777282; 2016 [501]	TZDs + albiglutide vs. albiglutide	SAEs	1	61	1	313	TZDs + albiglutide 30 mg: 1/61 (foot) Albiglutide 30 mg + sulfonylurea: 0/120 Albiglutide 30 mg + biguanide: 0/67 Albiglutide 30 mg + glinide: 0/65 Albiglutide 30 mg + α-glycoside Is: 1/61 (femur)
NCT01468181; 2015 [502]	TZDs + dulaglutide vs. dulaglutide	SAEs	1	66	1	328	TZDs + dulaglutide 0.75 mg SAEs: 1/66 (pelvic) Dulaglutide 0.75 mg + sulfonylurea SAEs: 0/131 Dulaglutide 0.75 mg + biguanide SAEs: 0/61 Dulaglutide 0.75 mg + glinide SAEs: 1/71 (ankle) Dulaglutide 0.75 mg + α-glycoside Is SAEs: 0/65
Araki 2015 [503]	TZDs + empagliflozin vs. empagliflozin	SAEs	2	273	4	887	TZDs + empagliflozin 10 mg: 0/137 TZDs + empagliflozin 25 mg: 2/136 (pelvic, ankle) Metformin + sulfonylurea: 0/63 Empagliflozin 10 mg + sulfonylurea: 1/136 (pelvic) Empagliflozin 25 mg + sulfonylurea: 1/137 (ankle) Empagliflozin 10 mg + biguanide: 1/68 (femur) Empagliflozin 25 mg + biguanide: 0/65 Empagliflozin 10 mg + glinide: 0/70 Empagliflozin 25 mg + glinide: 0/70 Empagliflozin 10 mg + α-glycoside Is: 0/69 Empagliflozin 25 mg + α-glycoside Is: 0/70 Empagliflozin 10 mg + DPP4-Is: 1/68 (femur) Empagliflozin 25 mg + DPP4-Is: 0/71
Yoon 2011† [507]	Pioglitazone + sitagliptin¶ vs. no-pioglitazone	SAEs	1	520	0	0	Pioglitazone 30 mg + sitagliptin: 1/261 humerus Pioglitazone: 0/259
Kashiwagi 2011† [508]	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	SAEs	3	134	0	0	Sitagliptin: 2/66 patella, rib Sitagliptin/placebo: 1/68 lower-limb
NCT01076075†; 2016 [509]	Pioglitazone/placebo + sitagliptin vs. no-pioglitazone	SAEs	1	422	0	0	Pioglitazone 30 mg/placebo: 1/212 skull Sitagliptin: 0/210
Rosenstock 2006† [510]	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	SAEs	1	353	0	0	Sitagliptin: 0/175 Placebo: 1/178 lower-limb
Fonseca 2013† [511]	Pioglitazone + sitagliptin + placebo vs. no- pioglitazone	SAEs	1	313	0	0	Sitagliptin: 0/157 Placebo: 1/156 patella
Charbonnel 2006† [512]	Pioglitazone + sitagliptin + glipizide/placebo vs. no-pioglitazone	SAEs	1	701	0	0	Glipizide/placebo: 1/237 traumatic fracture Sitagliptin: 0/464
Forst 2014† [513]	Pioglitazone + canagliflozin + sitagliptine/placebo vs. no-pioglitazone	SAEs	3	684	0	0	Canagliflozin 100 mg: 2/113 (2 periprosthetic fracture) Canagliflozin 300 mg: 1/114 (tibia)

							Sitagliptine/placebo: 0/230
Kovacs 2014† [514]	Pioglitazone + empagliflozin + sitagliptin + placebo vs. no-pioglitazone	SAEs	16	2705	0	0	Pioglitazone + empagliflozin 10 mg: 3/165 (humerus, hand, traumatic fracture) Pioglitazone + empagliflozin 25 mg: 3/165 (upper-limb, ankle, comminute fracture) Pioglitazone + placebo: 0/168 Metformin + placebo: 0/214 Metformin + sulfonylurea + placebo: 2/217 (femur, ankle) Empagliflozin 10 mg: 0/229 Empagliflozin 25 mg: 1/224 (upper-limb) Empagliflozin 10 mg + metformin: 2/206 (hip, tibia) Empagliflozin 25 mg + metformin: 2/217 (facial, comminute fracture) Empagliflozin 10 mg + metformin + sulfonylurea: 1/225 (multiple fracture) Empagliflozin 25 mg + metformin + sulfonylurea: 1/224 (femural neck) Sitagliptin 100 mg: 0/223 Placebo: 1/223 (tibia)
Philis-Tsimikas 2013† [515]	Pioglitazone + sitagliptin + insulin degludec vs. no-pioglitazone	SAEs	1	454	0	0	Insulin degludec: 1/226 hip Sitagliptin: 0/228
Nauck 2016† [516]	Pioglitazone + linagliptin¶ vs. no-pioglitazone	SAEs	1	936	0	0	Linagliptin 5 mg/pioglitazone 15 mg/linagliptin 5 mg/pioglitazone 30 mg: 0/126 Linagliptin 5 mg/pioglitazone 30 mg/linagliptin 5 mg/pioglitazone 30 mg: 1/126 (traumatic fracture) Linagliptin 5 mg/pioglitazone 45 mg/linagliptin 5 mg/pioglitazone 45 mg: 0/126 Pioglitazone 15 mg/pioglitazone 30 mg: 0/131 Pioglitazone 30 mg/pioglitazone 30 mg: 0/140 Pioglitazone 45 mg/pioglitazone 45 mg: 0/138 Linagliptin 5 mg/linagliptin 5 mg: 0/135
Gantz 2017† [517]	Pioglitazone/omarigliptin + placebo vs. no-pioglitazone	SAEs	2	580	0	0	Pioglitazone/Omarigliptin 25 mg + placebo + AHG: 2/191 (hand, fracture displacement) Omarigliptin 25 mg + TZDs: 0/65 Omarigliptin 25 mg + sulfonylurea: 0/126 Omarigliptin 25 mg + biguanide: 0/66 Omarigliptin 25 mg + glinide: 0/65 Omarigliptin 25 mg + α-glycoside Is: 0/67
Davies 2015† [520]	TZDs + liraglutide + placebo vs. no-TZDs	SAEs	1	844	0	0	Liraglutide 1.8 mg: 1/210 (spinal compression fracture) Liraglutide 3 mg: 0/422 Liraglutide + placebo: 0/212
Kiyosue 2018† [521]	TZDs + liraglutide + additional AHG vs. no-TZDs	SAEs	1	360	0	0	Liraglutide: 0/240 Additional AHG: 1/120 foot
Norwood 2012† [522]	TZDs + metformin + exenatide vs. no-TZDs	SAEs	1	134	0	0	TZDs ± metformin + exenatide: patella
Wysham 2014† [523]	Pioglitazone + exenatide + dulaglutide + placebo vs. no-pioglitazone	SAEs	2	978	0	0	Exenatide: 2/278 (humerus) Dulaglutide 0.75 mg: 0/280 Dulaglutide 1.5 mg: 0/279 Placebo: 0/141
NCT00765817†; 2015 [524]	Pioglitazone insulin glargine + exenatide + placebo vs. no-pioglitazone	SAEs	1	259	0	0	Exenatide: 0/137 Placebo: 1/122 ankle
Bode 2015† [525]	TZDs + canagliflozin + placebo vs. no-TZDs	SAEs	5	714	0	0	Canagliflozin 100 mg: 1/241 (ankle) Canagliflozin 300 mg: 1/236 (hip) Placebo: 3/237 (2 cervical vertebra, 1 hand)
Garber 2012† [527]	± Pioglitazone + insulin degludec + insulin glargine vs. no-pioglitazone	SAEs	7	1004	0	0	Insulin degludec: 3/753 (hip, humerus, ankle) Insulin glargine: 4/251 (humerus, radius, fibula, ankle)
Fulcher 2019† [528]	± Pioglitazone + insulin degludec/insulin aspart + biphasic insulin aspart vs. no-pioglitazone	SAEs	2	446	0	0	Insulin degludec/insulin aspart: 1/224 radius Biphasic insulin aspart: 1/222 upper-limb
Gross 2016† [529]	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	SAEs	1	476	0	0	Insulin lispr: 1/236 pelvic Insulin lispro + insulin glargine: 0/240

Abbreviations: *DPP4-Is*, Dipeptidyl peptidase-4 inhibitors; *F*, female; *M*, male; *SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG; §Multiple fractures per person; †these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-6. Studies results of spine fractures

Study	Treatment groups	Primary fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs and SAEs Low-energy, non-pathological	38 F: 19 M: 19 F: 16 M: 14	1939 F: 646 M: 1293 F: 646 M: 1293	18 F: 16 M: 2 F: 15 M: 2	1937 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 24 spine (7 lumbar, 12 thoracic, 5 cervical/sacrum) Pioglitazone M: 30 spine (17 lumbar, 10 thoracic, 3 cervical/sacrum) Placebo F: 24 spine (12 lumbar, 7 thoracic, 5 cervical/sacrum) Placebo M: 4 spine (2 lumbar, 2 thoracic, cervical/sacrum) Overall multiple fractures[§] 292 (155 F; 137 M) (176 (88F/88M pioglitazone) and (178 (73 F/45M placebo)
Dormandy 2005 [140]	Pioglitazone vs. placebo	AEs	6 F:6 M:0	2605 F:870 M:1735	0 F:0 M:0	2633 F:905 M:1728	Pioglitazone F: 6 spine Placebo F: 0 spine M NR
Home 2014 [472] NCT00839527	Pioglitazone + albiglutide vs. placebo	AEs and SAEs	0	548	1	115	Pioglitazone 30-45 mg + metformin ≥1500 mg + glimepiride 4 mg: 0/277 Albiglutide 30 mg + metformin ≥1500 mg + glimepiride 4 mg: 1/271 (SAEs: thoracic vertebra fracture) Metformin + glimepiride + placebo AEs: 0/115
Chou 2012 [345]	Pioglitazone + rivoglitazone vs. placebo	SAEs	1	1749	0	137	Pioglitazone 45 mg: 0/739 Rivoglitazone 1 mg: 0/269 Rivoglitazone 1.5 mg: 1/741 (spinal compression fracture) Placebo: 0/137
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	SAEs	F:1	F:114	F:0	F:112	Rosiglitazone 8 mg postmenopausal F (pathological fracture): lumbar spine Metformin (pathological fracture): 0
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs SAEs	14 F:8 M:6 49	2220 F:1078 M:1142 2220	9 F:4 M:5 36	2227 F:1075 M:1152 2227	Rosiglitazone F: 8 spine Rosiglitazone M: 6 spine Active control F: 4 spine Active control M: 5 spine NR
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	4 F:1 M:3	1456 F:645 M:811	3 F:2 M:1	2895 F:1195 M:1700	Rosiglitazone F: 1/645 spine; M: 3/811 Metformin F: 1/590 spine; M: 0/864 Glyburide F: 1/605 spine; M: 1/836
Gomis 2012 [498]	Pioglitazone/linagliptine[¶] vs. linagliptine	SAEs	0	589	1	1532	Pioglitazone 30 mg + linagliptine: 0 Linagliptine: spinal compression
NCT01204294; 2014 [499]	TZDs + linagliptin vs. linagliptin	SAEs	0	74	1	500	TZDs + linagliptin: 0/74 Sulfonylurea + metformin: 0/63 Sulfonylurea + linagliptin: 0/143 Biguanide + linagliptin: 1/82 (lumbar vertebra fracture) Glinide + linagliptin: 0/66 α-glycoside Is + metformin: 0/61 α-glycoside Is + linagliptin: 0/85
Kadowaki 2013[†] [519]	Pioglitazone/teneligliptin[¶] + placebo vs. no-pioglitazone	AEs	2	204	0	0	Pioglitazone + teneligliptin/teneligliptin: 2/103 thoracic vertebra fracture Pioglitazone + teneligliptin/placebo: 0/101
Davies 2015[†] [520]	TZDs + liraglutide + placebo vs. no-TZDs	SAEs	1	844	0	0	Liraglutide 1.8 mg: 1/210 (spinal compression fracture) Liraglutide 3 mg: 0/422 Liraglutide + placebo: 0/212
Bode 2015[†] [525]	TZDs + canagliflozin + placebo vs. no-TZDs	SAEs	2	714	0	0	Canagliflozin 100 mg: 0/241 Canagliflozin 300 mg: 0/236 Placebo: 2/237 (2 cervical vertebra)

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [§]Multiple fractures per person; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-7. Studies results of hip fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs and SAEs Low-energy, non-pathological	32 F: 15 M: 17 F: 10 M: 14	1939 F: 646 M: 1293 F: 646 M: 1293	25 F: 16 M: 9 F: 12 M: 6	1937 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: (11 hip, 8 pelvis) Pioglitazone M: (14 hip, 4 pelvis) Placebo F: (10 hip, 7 pelvis) Placebo M: (7 hip, 3 pelvis) Overall multiple hip fractures[§] 42 (25pioglitazone; 17placebo) (23 (9 F/14M in pioglitazone) and (16 (9F/7M in placebo) Overall multiple pelvis fractures[§] 22 (12pioglitazone; 10placebo) (12 (6F/3M pioglitazone) and (10 (7F/2M placebo)
Marder 2013 [347]	Pioglitazone vs. placebo	SAEs	1	129	0	127	Pioglitazone: hip
Dormandy 2005 [140]	Pioglitazone vs. placebo	AEs	2 F:2 M:0	2605 F:870 M:1735	0 F:0 M:0	2633 F:905 M:1728	Pioglitazone F: 2 hip Placebo F: 0 hip M NR
Gold 2010 [343]	Rosiglitazone vs. placebo	AEs and SAEs	1 F:1 M:0	331 129 71	1 F:1 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 1/166 (hip) Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: hip. SAEs: hip
GSK49635/351; 2008 [481]	Rosiglitazone vs. placebo	SAEs	0	30	1	30	Placebo: pubic rami
Comaschi 2007 [493]	Pioglitazone + sulfonylurea vs. metformin/glibenclamide[¶]	AEs	1	340	0	80	Pioglitazone: 1/170 hip arthroplasty Pioglitazone + metformin: 0/103 Pioglitazone + sulfonylurea: 0/67 Metformin + glibenclamide: 0/80
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs SAEs	0 F:0 M:0 49	2220 F:1078 M:1142 2220	4 F:1 M:3 36	2227 F:1075 M:1152 2227	Rosiglitazone F: 0 pelvis Rosiglitazone M: 0 pelvis Active control F: 1 pelvis Active control M: 3 pelvis NR
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	3 F:2 M:1	1456 F:645 M:811	5 F:4 M:1	2895 F:1195 M:1700	Rosiglitazone F: 2/645 hip, 0 pelvic; M: 1/811 hip Metformin F: 2/590 hip, 2 pelvic; M: 0/864 hip Glyburide F: 0/605 hip, 0 pelvic; M: 1/836 hip
Gomis 2012 [498]	Pioglitazone/linagliptine[¶] vs. linagliptine	SAEs	0	589	1	1532	Pioglitazone 30 mg + linagliptine: 0 Linagliptine: hip
NCT01468181; 2015 [502]	TZDs + dulaglutide vs. dulaglutide	AEs and SAEs	1	66	0	328	TZDs + dulaglutide 0.75 mg SAEs: 0/66 (pelvic) Dulaglutide 0.75 mg + sulfonylurea AEs: 0/131 Dulaglutide 0.75 mg + biguanide AEs: 0/61 Dulaglutide 0.75 mg + glinide SAEs: 0/71 Dulaglutide 0.75 mg + α-glycoside Is AEs: 0/65
Araki 2015 [503]	TZDs + empagliflozin vs. empagliflozin	SAEs	1	273	1	887	TZDs + empagliflozin 10 mg: 0/137 TZDs + empagliflozin 25 mg: 1/136 (pelvic) Metformin + sulfonylurea: 0/63 Empagliflozin 10 mg + sulfonylurea: 1/136 (pelvic) Empagliflozin 25 mg + sulfonylurea: 0/137 Empagliflozin 10 mg + biguanide: 0/68 Empagliflozin 25 mg + biguanide: 0/65 Empagliflozin 10 mg + glinide: 0/70 Empagliflozin 25 mg + glinide: 0/70 Empagliflozin 10 mg + α-glycoside Is: 0/69 Empagliflozin 25 mg + α-glycoside Is: 0/70 Empagliflozin 10 mg + DPP4-Is: 0/68 Empagliflozin 25 mg + DPP4-Is: 0/71
Kovacs 2014[†] [514]	Pioglitazone + empagliflozin + placebo + empagliflozin + sitagliptin + placebo vs. no-pioglitazone	SAEs	1	2705	0	0	Pioglitazone + empagliflozin 10 mg: 0/165 Pioglitazone + empagliflozin 25 mg: 0/165 Pioglitazone + placebo: 0/168 Metformin + placebo: 0/214 Metformin + sulfonylurea + placebo: 0/217 Empagliflozin 10 mg: 0/229 Empagliflozin 25 mg: 0/224 Empagliflozin 10 mg + metformin: 1/206 (hip)

							Empagliflozin 25 mg + metformin: 0/217 Empagliflozin 10 mg + metformin + sulfonylurea: 0/225 Empagliflozin 25 mg + metformin + sulfonylurea: 0/224 Sitagliptin 100 mg: 0/223 Placebo: 0/223
Philis-Tsimikas 2013[†] [515]	Pioglitazone + sitagliptin + insulin degludec vs. no-pioglitazone	SAEs	1	454	0	0	Insulin degludec: 1/226 hip Sitagliptin: 0/228
Bode 2015[†] [525]	TZDs + canagliflozin + placebo vs. no-TZDs	SAEs	1	714	0	0	Canagliflozin 100 mg: 0/241 Canagliflozin 300 mg: 1/236 (hip) Placebo: 0/237
Garber 2012[†] [527]	± Pioglitazone + insulin degludec + insulin glargine vs. no-pioglitazone	SAEs	1	1004	0	0	Insulin degludec: 1/753 hip Insulin glargine: 0/251
Gross 2016[†] [529]	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	SAEs	1	476	0	0	Insulin lispro SAEs: 1/236 pelvic Insulin lispro + insulin glargine: 0/240

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG, [§]Multiple fractures per person; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-8. Studies results of femur fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs and SAEs Low-energy, non-pathological	4 F: 3 M: 1 F: 10 M: 14	1939 F: 646 M: 1293 F: 646 M: 1293	3 F: 3 M: 0 F: 12 M: 6	1937 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 3 femur Pioglitazone M: 1 femur Placebo F: 4 femur Placebo M: 0 Overall multiple fractures[§] 8 (4pioglitazone; 4placebo) (4 (3F/1M pioglitazone) and (3 (3F/0M placebo)
GSK49653/334; 2008 [480]	Rosiglitazone vs. placebo	SAEs	0	277	1	278	Placebo IR SAEs: femoral neck
Wainstein 2012 [487]	Pioglitazone vs. metformin/sitagliptin[¶]	SAEs	0	256	1	261	Pioglitazone: 0/256 Metformin/sitagliptin: 1/261 femur
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs SAEs	10 F:7 M:3 49	2220 F:1078 M:1142 2220	8 F:7 M:1 36	2227 F:1075 M:1152 2227	Rosiglitazone F: 7 femur/hip Rosiglitazone M: 3 femur/hip Active control F: 7 femur/hip Active control M: 1 femur/hip NR
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	2 F:2 M:0	1456 F:645 M:811	2 F:0 M:2	2895 F:1195 M:1700	Rosiglitazone F: 2/645femur; M: 0/811 Metformin F: 0/590 femur; M: 2/864 Glyburide F: 0/605 femur; M: 0/836
AVM100264; 2008 [495]	Rosiglitazone + metformin vs. metformin + sulfonylurea	SAEs	1	294	1	301	Rosiglitazone + metformin: femur Metformin + sulfonylurea: femoral neck
Gomis 2012 [498]	Pioglitazone/linagliptine[¶] vs. linagliptine	SAEs	0	589	1	1532	Pioglitazone 30 mg + linagliptine: 0 Linagliptine: femur
NCT01777282; 2016 [501]	TZDs + albiglutide vs. albiglutide	SAEs	0	61	1	313	TZDs + albiglutide 30 mg: 0/61 Albiglutide 30 mg + sulfonylurea: 0/120 Albiglutide 30 mg + biguanide: 0/67 Albiglutide 30 mg + glinide: 0/65 Albiglutide 30 mg + α-glycoside Is: 1/61 (femur)
Araki 2015 [503]	TZDs + empagliflozin vs. empagliflozin	SAEs	0	273	2	887	TZDs + empagliflozin 10 mg: 0/137 TZDs + empagliflozin 25 mg: 0/136 Metformin + sulfonylurea: 0/63 Empagliflozin 10 mg + sulfonylurea: 0/136 Empagliflozin 25 mg + sulfonylurea: 0/137 Empagliflozin 10 mg + biguanide: 1/68 (femur) Empagliflozin 25 mg + biguanide: 0/65 Empagliflozin 10 mg + glinide: 0/70 Empagliflozin 25 mg + glinide: 0/70 Empagliflozin 10 mg + α-glycoside Is: 0/69 Empagliflozin 25 mg + α-glycoside Is: 0/70 Empagliflozin 10 mg + DPP4-Is: 1/68 (femur) Empagliflozin 25 mg + DPP4-Is: 0/71
Forst 2014[†] [513]	Pioglitazone + canagliflozin + sitagliptine/placebo vs. no-pioglitazone	SAEs	2	684	0	0	Canagliflozin 100 mg: 2/113 (2 periprosthetic fracture) Canagliflozin 300 mg: 0/114 Sitagliptine/placebo: 0/230
Kovacs 2014[†] [514]	Pioglitazone + empagliflozin + placebo + empagliflozin + sitagliptin + placebo vs. no-pioglitazone	SAEs	2	2705	0	0	Pioglitazone + empagliflozin 10 mg: 0/165 Pioglitazone + empagliflozin 25 mg: 0/165 Pioglitazone + placebo: 0/168 Metformin + placebo: 0/214 Metformin + sulfonylurea + placebo: 1/217 (femur) Empagliflozin 10 mg: 0/229 Empagliflozin 25 mg: 0/224 Empagliflozin 10 mg + metformin: 0/206 Empagliflozin 25 mg + metformin: 0/217 Empagliflozin 10 mg + metformin + sulfonylurea: 0/225 Empagliflozin 25 mg + metformin + sulfonylurea: 1/224 (femural neck) Sitagliptin 100 mg: 0/223

			Placebo: 0/223

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report; *SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG, [§]Multiple fractures per person; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-9. Studies results of upper-limb fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs and SAEs Low-energy, non-pathological	70 F: 38 M: 32 F: 34 M: 22	1939 F: 646 M: 1293 F: 646 M: 1293	55 F: 26 M: 29 F: 24 M: 22	1937 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 59 upper-limb (16 humerus, 20 radius, 7 ulna, 4 carpal, 12 metacarpal/phalange) Pioglitazone M: 34 upper-limb (9 humerus, 10 radius, 1 ulna, 3 carpal, 11 metacarpal/phalange) Placebo F: 34 upper-limb (7 humerus, 12 radius, 7 ulna, 2 carpal, 6 metacarpal/phalange) Placebo M: 34 upper-limb (10 humerus, 7 radius, 6 ulna, 2 carpal, 9 metacarpal/phalange) Overall multiple farcture[$] 161 (93pioglitazone; 68placebo) (70 (38F/32M pioglitazone) and (55 (26F/29M placebo)
Dormandy 2005 [140]	Pioglitazone vs. placebo	AEs	7 F:7 M:0	2605 F:870 M:1735	1 F:1 M:0	2633 F:905 M:1728	Pioglitazone F: 7 proximal-limb Placebo F: 1 proximal-limb M NR
NCT00722371; 2015 [474]	Pioglitazone + sitagliptin[¶] vs. sitagliptin + placebo	SAEs	1	1384	0	231	Pioglitazone: 0/693 Pioglitazone/sitagliptin: 1/691 upper-limb Sitagliptin: 0/231
Gold 2010 [343]	Rosiglitazone vs. placebo	AEs	0 F:0 M:0	331 129 71	1 F:1 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 0/166 Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: upper-limb.
GSK49653/334; 2008 [480]	Rosiglitazone vs. placebo	SAEs	0	277	1	278	Placebo SAEs: upper-limb
Nissen 2008 [146]	Pioglitazone vs. glimepiride	AEs	1 F:6 M:2	270 F:84 M:186	0 F:0 M:0	273 F:93 M:180	Pioglitazone: upper-limb NR by gender
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs SAEs	86 F:63 M:23 49	2220 F:1078 M:1142 2220	55 F:36 M:19 36	2227 F:1075 M:1152 2227	Rosiglitazone F: 63 upper-limb Rosiglitazone M: 23 upper-limb Active control F: 36 upper-limb Active control M: 19 upper-limb NR
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	3 F:3 M:0	1456 F:645 M:811	5 F:3 M:2	2895 F:1195 M:1700	Rosiglitazone F: 3/645 upper-limb; M: 0/811 Metformin F: 2/590 upper-limb; M: 1/864 Glyburide F: 1/605 upper-limb; M: 1/836
Kovacs 2014[†] [514]	Pioglitazone + empagliflozin + placebo vs. empagliflozin + sitagliptin + placebo	SAEs	2	2705	0	0	Pioglitazone + empagliflozin 10 mg: 0/165 Pioglitazone + empagliflozin 25 mg: 1/165 (upper-limb) Pioglitazone + placebo: 0/168 Metformin + placebo: 0/214 Metformin + sulfonylurea + placebo: 0/217 Empagliflozin 10 mg: 0/229 Empagliflozin 25 mg: 1/224 (upper-limb) Empagliflozin 10 mg + metformin: 0/206 Empagliflozin 25 mg + metformin: 0/217 Empagliflozin 10 mg + metformin + sulfonylurea: 0/225 Empagliflozin 25 mg + metformin + sulfonylurea: 0/224 Sitagliptin 100 mg: 0/223 Placebo: 0/223
Rosenstock 2012[†] [526]	Pioglitazone + dapagliflozin + placebo vs. no-pioglitazone	AEs	1 F:0 M:1	420 F:212 M:208	0 F:0 M:0	0 F:0 M:0	Pioglitazone + dapagliflozin: 1/281 limb fractures F: 0 M: hand Pioglitazone + placebo: 0/139
Fulcher 2019[†] [528]	± Pioglitazone + insulin degludec/insulin aspart + biphasic insulin aspart vs. no-pioglitazone	SAEs	1	446	0	0	Insulin degludec/insulin aspart: 0/224 Biphasic insulin aspart: 1/222 upper-limb

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [$]Multiple fractures per person; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-10. Studies results of wrist fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Bray 2013 [352]	Pioglitazone vs. placebo	AEs*	3	303	0	299	Pioglitazone: 3 traumatic fractures (wrist) Placebo: 0 wrist
Gold 2010 [343]	Rosiglitazone vs. placebo	AEs	0 F:0 M:0	331 129 71	1 F:1 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 0/166 Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: wrist.
Perez 2009 [486]	Pioglitazone/metformin¶ vs. metformin	AEs	1 F:1 M:0	390 F:234 M:156	1 F:0 M:1	210 F:112 M:98	Pioglitazone 15 mg/metformin 850 mg BID F: 1/200 (wrist) Pioglitazone 15 mg: 0/190 Metformin 850 mg BID M: 1/210 (traumatic wrist)
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	SAEs	F:1	F:114	F:1	F:112	Rosiglitazone 8 mg postmenopausal F (pathological fracture): wrist (fall) Metformin (pathological fracture): wrist (fall)
Nissen 2008 [146]	Pioglitazone vs. glimepiride	AEs	1 F:6 M:2	270 F:84 M:186	0 F:0 M:0	273 F:93 M:180	Pioglitazone: wrist NR by gender
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	7 F:5 M:2	1456 F:645 M:811	11 F:7 M:4	2895 F:1195 M:1700	Rosiglitazone F: 5/645; M: 2/811 Metformin F: 3/590; M: 2/864 Glyburide F: 4/605; M: 2/836
NCT00367055; 2010 [494]	Rosiglitazone + metformin¶ vs. gliclazide + metformin¶	SAEs	0	43	1	41	Gliclazide + metformin: wrist
Gross 2016† [529]	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	AEs	1	476	0	0	Insulin lispro: 1//236 wrist Insulin lispro + insulin glargine: 0/240

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG; †these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-11. Studies results of lower-limb fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs and SAEs Low-energy, non-pathological	77 F: 38 M: 39 61 F: 35 M: 26	1939 F: 646 M: 1293 1939 F: 646 M: 1293	43 F: 25 M: 18 35 F: 23 M: 12	1937 F: 692 M: 1245 1937 F: 692 M: 1245	Pioglitazone F: 62 distal-lower-limb (1 patella, 23 fibula, 17 tibia, 4 tarsal, 17 metatarsal/phalange) Pioglitazone M: 55 distal-lower-limb (2 patella, 14 fibula, 17 tibia, 5 tarsal, 17 metatarsal/phalange) Placebo F: 33 distal-lower-limb (2 patella, 9 fibula, 7 tibia, 1 tarsal, 14 metatarsal/phalange) Placebo M: 20 distal-lower-limb (patella, 6 fibula, 4 tibia, tarsal, 10 metatarsal/phalange) Overall multiple hip fractures[§] 170 (117pioglitazone; 53placebo) (23 (38F/39M pioglitazone) and (16 (25F/18M placebo)
Dormandy 2005 [140]	Pioglitazone vs. placebo	AEs	22 F:22 M:0	2605 F:870 M:1735	11 F:11 M:0	2633 F:905 M:1728	Pioglitazone F: 22 distal-limbs Placebo F: 11 distal-limbs M NR
Harrison 2012 [478]	Pioglitazone vs. no-TZDs	SAEs	1	77	0	73	Pioglitazone: lower-limb
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	SAEs	F:1	F:114	F:0	F:112	Rosiglitazone 8 mg postmenopausal F (pathological fracture): lower-limb (fall) Metformin (pathological fracture): 0
Nissen 2008 [146]	Pioglitazone vs. glimepiride	AEs	2 F:6 M:2	270 F:84 M:186	0 F:0 M:0	273 F:93 M:180	Pioglitazone: 2 lower-limb NR by gender
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs SAEs	70 F:47 M:23 49	2220 F:1078 M:1142 2220	27 F:16 M:11 36	2227 F:1075 M:1152 2227	Rosiglitazone F: 47 distal-lower-limb Rosiglitazone M: 23 distal-lower-limb Active control F: 16 distal-lower-limb Active control M: 11 distal-lower-limb NR
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	2 F:1 M:1	1456 F:645 M:811	2 F:2 M:0	2895 F:1195 M:1700	Rosiglitazone F: 1/645 lower-limb; M: 1/811 Metformin F: 2/590 lower-limb; M: 0/864 Glyburide F: 0/605 lower-limb; M: 0/836
Gomis 2012 [498]	Pioglitazone/linagliptine[¶] vs. linagliptine	SAEs	0	589	1	1532	Pioglitazone 30 mg + linagliptine: 0 Linagliptine: lower-limb
Kashiwagi 2011[†] [508]	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	SAEs	1	134	0	0	Sitagliptin: 0/133 Sitagliptin/placebo: 1/68 lower-limb
Rosenstock 2006[†] [510]	Pioglitazone + sitagliptin + placebo vs. no-pioglitazone	SAEs	1	353	0	0	Sitagliptin: 0/175 Placebo: 1/178 lower-limb
Rosenstock 2012[†] [526]	Pioglitazone + dapagliflozin + placebo vs. no-pioglitazone	AEs	1 F:1 M:0	420 F:212 M:208	0 F:0 M:0	0 F:0 M:0	Pioglitazone + dapagliflozin: 1/281 limb fracture F: foot M: 0 Pioglitazone + placebo: 0/139
Gross 2016[†] [529]	± Pioglitazone + insulin lispro + insulin glargine vs. no-pioglitazone	AEs	1	476	0	0	Insulin lispro: 0/236 Insulin lispro + insulin glargine: 1/240 lower-limb

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [§]Multiple fractures per person; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-12. Studies results of ankle fractures

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Simuni 2015 [346]	Pioglitazone vs. placebo	SAEs	1	139	0	71	Pioglitazone 15 mg: 1/72 (ankle) Pioglitazone 45 mg: 0/67
Grey 2014 [351]	Pioglitazone vs. placebo	AEs	2	43	0	43	Pioglitazone: 2 ankle
Bray 2013 [352]	Pioglitazone vs. placebo	AEs*	0	303	3	299	Pioglitazone: 0 ankle Placebo: 3 traumatic fractures (ankle)
Bone 2013 [350]	Pioglitazone vs. placebo	AEs and SAEs	F:0	F:78	F:2	F:78	Pioglitazone postmenopausal F AEs: 0 Placebo postmenopausal F AEs (pathological fracture): ankle. SAEs (pathological fracture): ankle
Home 2014 [472] NCT00839527	Pioglitazone + albiglutide vs. placebo	SAEs	1	548	0	115	Pioglitazone 30-45 mg + metformin ≥1500 mg + glimepiride 4 mg: 1/277 (SAEs: ankle) Albiglutide 30 mg + metformin ≥1500 mg + glimepiride 4 mg: 0/271 Metformin + glimepiride + placebo AEs: 0/115
Borges 2011 [349]	Rosiglitazone/metformin¶ vs. metformin	AEs and SAEs	2 F:2 M:0	344 F:160 M:184	0 F:0 M:0	334 F:158 M:176	Rosiglitazone/metformin AEs: 0 Rosiglitazone/metformin F SAEs: 2 ankle Metformin AEs: 0
Jain 2006 [490]	Pioglitazone vs. glyburide	SAEs	0	251	2	251	Glyburide: ankle
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs	7 F:5 M:2	1456 F:645 M:811	15 F:9 M:6	2895 F:1195 M:1700	Rosiglitazone F: 5/645; M: 2/811 Metformin F: 6/590; M: 3/864 Glyburide F: 3/605; M: 3/836
NCT01204294; 2014 [499]	TZDs + linagliptin vs. linagliptin	SAEs	0	74	1	500	TZDs + linagliptin: 0/74 Sulfonylurea + metformin: 0/63 Sulfonylurea + linagliptin: 1/143 (ankle) Biguanide + linagliptin: 0/82 Glinide + linagliptin: 0/66 α-glycoside Is + metformin: 0/61 α-glycoside Is + linagliptin: 0/85
Araki 2015 [503]	TZDs + empagliflozin vs. empagliflozin	SAEs	1	273	1	887	TZDs + empagliflozin 10 mg: 0/137 TZDs + empagliflozin 25 mg: 1/136 (ankle) Metformin + sulfonylurea: 0/63 Empagliflozin 10 mg + sulfonylurea: 0/136 Empagliflozin 25 mg + sulfonylurea: 1/137 (ankle) Empagliflozin 10 mg + biguanide: 0/68 Empagliflozin 25 mg + biguanide: 0/65 Empagliflozin 10 mg + glinide: 0/70 Empagliflozin 25 mg + glinide: 0/70 Empagliflozin 10 mg + α-glycoside Is: 0/69 Empagliflozin 25 mg + α-glycoside Is: 0/70 Empagliflozin 10 mg + DPP4-Is: 0/68 Empagliflozin 25 mg + DPP4-Is: 0/71
Ruilope 2014† [505]	Pioglitazone + aleglitazar vs. no-pioglitazone	AEs	1	301	0	0	Pioglitazone 45 mg: 0/152 Aleglitazar 0.15 mg: 1/149 ankle
Kovacs 2014† [514]	Pioglitazone + empagliflozin + placebo + empagliflozin + sitagliptin + placebo vs. no-pioglitazone	SAEs	2	2705	0	0	Pioglitazone + empagliflozin 10 mg: 0/165 Pioglitazone + empagliflozin 25 mg: 1/165 (ankle) Pioglitazone + placebo: 0/168 Metformin + placebo: 0/214 Metformin + sulfonylurea + placebo: 1/217 (ankle) Empagliflozin 10 mg: 0/229 Empagliflozin 25 mg: 0/224 Empagliflozin 10 mg + metformin: 0/206 Empagliflozin 25 mg + metformin: 0/217 Empagliflozin 10 mg + metformin + sulfonylurea: 0/225 Empagliflozin 25 mg + metformin + sulfonylurea: 0/224 Sitagliptin 100 mg: 0/223 Placebo: 0/223
NCT00765817†; 2015 [524]	Pioglitazone + insulin glargine + exenatide + placebo vs. no-pioglitazone	SAEs	1	259	0	0	Exenatide: 0/137 Placebo: 1/122 ankle
Gomis 2012 [498]	Pioglitazone/linagliptine¶ vs. linagliptine	SAEs	0	589	1	1532	Pioglitazone 30 mg + linagliptine: 0

							Linagliptine: ankle
NCT01468181; 2015 [502]	TZDs + dulaglutide vs. dulaglutide	AEs AEs AEs SAEs AEs	0	66	1	328	TZDs + dulaglutide 0.75 mg: 0/66 Dulaglutide 0.75 mg + sulfonylurea: 0/131 Dulaglutide 0.75 mg + biguanide: 0/61 Dulaglutide 0.75 mg + glinide: 1/71 (ankle) Dulaglutide 0.75 mg + α-glycoside Is: 0/65
Bode 2015[†] [525]	TZDs + canagliflozin + placebo vs. no-TZDs	SAEs	1	714	0	0	Canagliflozin 100 mg: 1/241 (ankle) Canagliflozin 300 mg: 0/236 Placebo: 0/237
Garber 2012[†] [527]	± Pioglitazone + insulin degludec + insulin glargine vs. no-pioglitazone	SAEs	2	1004	0	0	Insulin degludec: 1/753 ankle Insulin glargine: 1/251 ankle

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [†]these studies report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-13. Studies results of adverse events fractures by gender

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	AEs Low-energy High-energy Non-pathologic Low-energy, non-pathologic	133 F: 64 M: 64 F: 88 M: 90 F: 6 M: 29 F: 96 M: 119 F: 88 M: 88	1939 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293	94 F: 48 M: 44 F: 73 M: 46 F: 4 M: 18 F: 79 M: 62 F: 73 M: 4	1937 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 59 upper-limb (16 humerus, 20 radius, 7 ulna, 4 carpal, 12 metacarpal/phalange), 14 proximal-lower-limb (11 hip, 8 pelvis, 3 femur, 24 spine (7 lumbar, 12 thoracic, 5 cervical/sacrum)), 6 rib, 62 distal-lower-limb (1 patella, 23 fibula, 17 tibia, 4 tarsal, 17 metatarsal/phalange), 13 other (4 skull/face, 1 scapula, 0 clavicle) Pioglitazone M: 34 upper-limb (9 humerus, 10 radius, 1 ulna, 3 carpal, 11 metacarpal/phalange), 15 proximal-lower-limbs (14 hip, 4 pelvis, 1 femur, 30 spine (17 lumbar, 10 thoracic, 3 cervical/sacrum)), 43 rib, 55 distal-lower-limb (2 patella, 14 fibula, 17 tibia, 5 tarsal, 17 metatarsal/phalange), 21 other (13 skull/face, 1 scapula, 3 clavicle) Placebo F: 34 upper-limb (7 humerus, 12 radius, 7 ulna, 2 carpal, 6 metacarpal/phalange), 14 proximal-lower-limb (10 hip, 7 pelvis, 4 femur, 24 spine (12 lumbar, 7 thoracic, 5 cervical/sacrum)), 12 rib, 33 distal-lower-limb (2 patella, 9 fibula, 7 tibia, 1 tarsal, 14 metatarsal/phalange), 11 other (2 skull/face, scapula, 2 clavicle) Placebo M: 34 upper-limb (10 humerus, 7 radius, 6 ulna, 2 carpal, 9 metacarpal/phalange), 7 proximal-lower-limb (7 hip, 3 pelvis, femur, 4 spine (2 lumbar, 2 thoracic, 0 cervical/sacrum)), 17 rib, 20 distal-lower-limb (patella, 6 fibula, 4 tibia, tarsal, 10 metatarsal/phalange), 15 other (9 skull/face, 0 scapula, 3 clavicle) Overall multiple fractures[§] 190 (94 F; 96 M) (128 (64F/64M pioglitazone) and (92 (48F/44M placebo)
Bone 2013 [350]	Pioglitazone vs. placebo	AEs	F:1	F:78	F:3	F:78	Pioglitazone postmenopausal F (pathological fracture): radius, metacarpus Placebo postmenopausal F (pathological fracture): ankle, lateral malleolus, metatarsal
Dormandy 2005 [94]	Pioglitazone vs. placebo	AEs	74 F:44 M:30	2605 F:870 M:1735	60 F:23 M:37	2633 F:905 M:1728	Pioglitazone F: 6 spine, 2 hip, 7 proximal-limbs, 22 distal-limbs, 7 undefined limb, 2 osteoporotic/pathological Placebo F: 0 spine, 0 hip, 1 proximal-limbs, 11 distal-limbs, 4 undefined limb, 2 osteoporotic/pathological M NR
Gold 2010 [343]	Rosiglitazone vs. placebo	AEs	2 F:2 M:0	331 129 71	3 F:3 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 2/166 (hip, hand) Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: hip, upper arm, wrist.
Gruntmanis 2010 [479]	Rosiglitazone vs. placebo	AEs	2 F:1 M:1	56 F:23 M:33	0 F:0 M:0	55 F:22 M:33	Rosiglitazone F: left humerus (fall) M: rib (fall)
Bach 2013 [342]	Rosiglitazone vs. no-TZDs	Bone fracture	82 50 F:29 M:21	1084 680 F:210 M:470	74 45 F:18 M:27	1076 680 F:210 M:470	NR
Seufert J (b) 2008 [484] [485]	Pioglitazone vs. metformin	AEs	0 F:0 M:0	319 F:148 M:171	2 F:1 M:1	320 F:145 M:175	NR
Perez 2009 [486]	Pioglitazone/metformin[¶] vs. metformin	AEs	1 F:1 M:0	390 F:234 M:156	1 F:0 M:1	210 F:112 M:98	Pioglitazone 15 mg/metformin 850 mg BID F: 1/200 (wrist) Pioglitazone 15 mg: 0/190 Metformin 850 mg BID M: 1/210 (traumatic wrist)
Borges 2011 [349]	Rosiglitazone/metformin[¶] vs. metformin	AEs	5 F:5 M:0	344 F:160 M:184	4 F:3 M:1	334 F:158 M:176	Rosiglitazone/metformin AEs: 5 Rosiglitazone/metformin F SAEs: 2 ankle Metformin AEs: 4
Tolman 2009 [489]	Pioglitazone vs. glibenclamide (glyburide)	AEs	30 F:16 M:14	1051 F:450 M:601	27 F:13 M:14	1046 F:465 M:581	NR
Nissen 2008 [146]	Pioglitazone vs. glimepiride	AEs	8 F:6 M:2	270 F:84 M:186	0 F:0 M:0	273 F:93 M:180	Pioglitazone: upper-limb, 2 lower-limb, hand, facial,2 humerus, wrist, metacarpal, rib, malleolar, 2 foot NR by gender
Seufert J (a) 2008 [484] [492]	Pioglitazone vs. gliclazide	AEs	1 F:1 M:0	317 F:156 M:161	1 F:1 M:0	313 F:159 M:154	NR
Home 2009 [125]	Rosiglitazone vs. metformin + sulfonylurea (active control)	AEs	185 F:124 M:61	2220 F:1078 M:1142	118 F:68 M:50	2227 F:1075 M:1152	Rosiglitazone F: 8 spine, 7 femur/hip, 0 pelvis, 63 upper-limb, 47 distal-lower-limb, 11 other Rosiglitazone M: 6 spine, 3 femur/hip, 0 pelvis, 23 upper-limb, 23 distal-lower-limb, 14 other Active control F: 4 spine, 7 femur/hip, 1 pelvis, 36 upper-limb, 16 distal-lower-limb, 1 other Active control M: 5 spine, 1 femur/hip, 3 pelvis, 19 upper-limb, 11 distal-lower-limb, 15 other
Kahn 2008 [159]	Rosiglitazone vs. metformin + glyburide	AEs High or low-energy Pathological/osteoporotic	92 F:60 M:32 F: 7 M: 0	1456 F:645 M:811 F:645 M:811	108 F:51 M:57 F: 10 M: 0	2895 F:1195 M:1700 F:1195	Rosiglitazone F: 1spine, 22 upper-limb (3 upper-limb, 0 forearm, 5 humerus, 1 radius, 8 hand, 5 wrist, 1 clavicle), 36 lower-limb (2 hip, 0 pelvic, 2 femur, 1 lower-limb, 1 tibia, 3 fibula, 5 ankle, 1 patella, 22 foot), 4 thoracic cage, 1 skull and facial, 0 not specific (60/645 total AEs)

			F: 10 M: 0	F:645 M:811	F: 7 M: 0	M:1700 F:1195 M:1700	Rosiglitazone M: 3 spine, 10 upper-limb (0 upper-limb, 2 humerus, 1 radius, 6 hand, 2 wrist, 0 clavicle), 10 lower-limb (1 hip, 0 femur, 1 lower-limb, 2 tibia, 2 fibula, 2 ankle, 0 patella, 3 foot), 9 thoracic cage, 0 skull and facial, 2 not specific (32/811 total AEs) Metformin F: 1 spine, 10 upper-limb (2 upper-limb, 0 forearm, 0 humerus, 1 radius, 4 hand, 3 wrist, 0 clavicle), 18 lower-limb (2 hip, 2 pelvic, 0 femur, 2 lower-limb, 0 tibia, 2 fibula, 6 ankle, 1 patella, 7 foot), 2 thoracic cage, 0 skull and facial, 0 not specific (30/590 total AEs) Metformin M: 0 spine, 7 upper-limb (1 upper-limb, 0 humerus, 2 radius, 3 hand, 2 wrist, 1 clavicle), 13 lower-limb (0 hip, 2 femur, 0 lower-limb, 0 tibia, 1 fibula, 3 ankle, 0 patella, 8 foot), 8 thoracic cage, 1 skull and facial, 1 not specific (29/864 total AEs) Glyburide F: 1 spine, 9 upper-limb (1 upper-limb, 1 forearm, 0 humerus, 2 radius, 1 hand, 4 wrist, 0 clavicle), 8 lower-limb (0 hip, 0 pelvic, 0 femur, 0 lower-limb, 1 tibia, 0 fibula, 3 ankle, 0 patella, 4 foot), 1 thoracic cage, 1 skull and facial, 2 not specific (21/605 total AEs) Glyburide M: 1spine, 10 upper-limb (1 upper-limb, 3 humerus, 3 radius, 0 hand, 2 wrist, 2 clavicle), 16 lower-limb (1 hip, 0 femur, 0 lower-limb, 0 tibia, 0 fibula, 3 ankle, 1 patella, 11 foot), 2 thoracic cage, 1 skull and facial, 1 not specific (28/836 total AEs)
Rosenstock 2012[†] [526]	Pioglitazone + dapagliflozin + placebo vs. no-pioglitazone	AEs	2 F:1 M:1	420 F:212 M:208	0 F:0 M:0	0 F:0 M:0	Pioglitazone + dapagliflozin: 2/281 limb fracture F: foot M: hand Pioglitazone + placebo: 0/139

Abbreviations: *AEs*, adverse event; *F*, female; *M*, male; *NR*, not report*; TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [§]Multiple fractures per person; [†]this study report fractures in both groups however all their participants had been exposed to TZDs.

Supplemental Table 2-14. Studies results of serious adverse events fractures by gender

Study	Treatment groups	Fracture outcomes	TZDs		Controls		Fracture per treatment allocation groups
			Events	Total	Events	Total	
Kernan and Viscoli 2016 [141]	Pioglitazone vs. placebo	SAEs Low-energy High-energy Non-pathologic Low-energy, non-pathologic Serious, low-energy, non-pathologic	F: 41 M: 58 F: 88 M: 90 F: 6 M: 29 F: 96 M 119 F: 88 M 88 F: 35 M: 41	F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293 F: 646 M: 1293	F: 38 M: 24 F: 73 M: 46 F: 4 M: 18 F: 79 M: 62 F: 73 M: 45 F: 37 M: 15	F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245 F: 692 M: 1245	Pioglitazone F: 59 upper-limb (16 humerus, 20 radius, 7 ulna, 4 carpal, 12 metacarpal/phalange), 14 proximal-lower-limb (11 hip, 8 pelvis, 3 femur, 24 spine (7 lumbar, 12 thoracic, 5 cervical/sacrum)), 6 rib, 62 distal-lower-limb (1 patella, 23 fibula, 17 tibia, 4 tarsal, 17 metatarsal/phalange), 13 other (4 skull/face, 1 scapula, 0 clavicle) Pioglitazone M: 34 upper-limb (9 humerus, 10 radius, 1 ulna, 3 carpal, 11 metacarpal/phalange), 15 proximal-lower-limb (14 hip, 4 pelvis, 1 femur, 30 spine (17 lumbar, 10 thoracic, 3 cervical/sacrum)), 43 rib, 55 distal-lower-limb (2 patella, 14 fibula, 17 tibia, 5 tarsal, 17 metatarsal/phalange), 21 other (13 skull/face, 1 scapula, 3 clavicle) Placebo F: 34 upper-limb (7 humerus, 12 radius, 7 ulna, 2 carpal, 6 metacarpal/phalange), 14 proximal-lower-limb (10 hip, 7 pelvis, 4 femur, 24 spine (12 lumbar, 7 thoracic, 5 cervical/sacrum)), 12 rib, 33 distal-lower-limb (2 patella, 9 fibula, 7 tibia, 1 tarsal, 14 metatarsal/phalange), 11 other (2 skull/face, scapula, 2 clavicle) Placebo M: 34 upper-limb (10 humerus, 7 radius, 6 ulna, 2 carpal, 9 metacarpal/phalange), 7 proximal-lower-limb (7 hip, 3 pelvis, femur, 4 spine (2 lumbar, 2 thoracic, 0 cervical/sacrum)), 17 rib, 20 distal-lower-limb (patella, 6 fibula, 4 tibia, tarsal, 10 metatarsal/phalange), 15 other (9 skull/face, 0 scapula, 3 clavicle) Overall multiple fractures[§] 178 (77 F; 101 M) (99 (41F/58M pioglitazone) and (99 (38F/24M placebo)
Bone 2013 [350]	Pioglitazone vs. placebo	SAEs	F:0	F:78	F:1	F:78	Pioglitazone postmenopausal F: 0 Placebo postmenopausal F (pathological fracture): ankle
Gold 2010 [343]	Rosiglitazone vs. placebo	SAEs	0 F:0 M:0	331 129 71	1 F:1 M:0	165 60 40	Rosiglitazone 2 mg F AEs: 2/166 (hip, hand) Rosiglitazone 2 mg AEs: 0/165 Placebo F AEs: hip, upper arm, wrist. SAEs: hip
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	SAEs	F:5	F:114	F:1	F:112	Rosiglitazone 8 mg postmenopausal F (pathological fractures): lumbar spine, wrist (fall), fingers (fall), lower leg (fall), toes (trauma) Metformin (pathological fractures): wrist (fall)
Borges 2011 [349]	Rosiglitazone/metformin[¶] vs. metformin	SAEs	2 F:2 M:0	344 F:160 M:184	0 F:0 M:0	334 F:158 M:176	Rosiglitazone/metformin: 0 Rosiglitazone/metformin F: 2 ankle Metformin: 0

Abbreviations: *F*, female; *M*, male; *NR*, not report*; SAEs*, *serious* adverse events; *TZD*, thiazolidinedione.
Note: [¶] Novel treatment of fixed-dose combination of 2 different classes of AHG; [§]Multiple fractures per person.

Supplemental Table 2-15. Studies results of fractures and bone mineral density

Study	Treatment groups	Population	Mean age‡	TZDs Dosage‡ mg/day	Percentage of changes in bone mineral density level, mean (SD)							
					Total body BMD		Hip		Lumbar spine		Femoral neck	
					TZDs	Controls	TZDs	Controls	TZDs	Controls	TZDs	Controls
Grey 2014 [351]	Pioglitazone vs. placebo	T2DM or impaired glucose tolerance	64.0	15-30	*n*=43 −1.0 (NR)	*n*=43 0.1 (NR)	*n*=43 −1.4 (2.7)	*n*=43 −0.2 (1.7)	*n*=43 −1.1 (3.4)	*n*=43 −0.4 (3.1)	NR	NR
Bray 2013 [352]	Pioglitazone vs. placebo	Impaired glucose tolerance with one risk factor of T2DM	53.0	30-45	NR	NR	NR	NR	*n*=213 −1.4 (13.14)	*n*=228 0.5 (15.10)	NR	NR
Bone 2013 [350]	Pioglitazone vs. placebo	Postmenopausal with impaired fasting glucose	59.0	30-45	*n*=59 −0.080 (NR)	*n*=61 −0.070 (NR)	NR	NR	*n*=59 −0.77 (2.84)	*n*=60 0.20 (2.87)	*n*=58 −0.64 (3.35)	*n*=61 0.21 (3.36)
Bilezikian 2013 [348]	Rosiglitazone vs. metformin	Postmenopausal T2DM	64.0	8	NR	NR	*n*=70 −1.62 (3.230)	*n*=78 −0.72 (3.347)	*n*=70 −1.41 (3.481)	*n*=76 −0.04 (3.653)	*n*=70 −1.47 (4.359)	*n*=78 0.22 (4.522)
Borges 2011 [349]	Rosiglitazone/Metformin ¶ vs. metformin	T2DM naive to oral AHGs	51.5	4-8	*n*=87 0.11 (NR)	*n*=87 1.1 (NR)	*n*=87 −1.5 (3.27)	*n*=87 0 (3.27)	*n*=87 −2.1 (5.04)	*n*=87 0.1 (5.04)	*n*=87 −1.4 (3.64)	*n*=87 −0.7 (3.64)
	Female	T2DM naive to oral AHGs	51.5	4-8	*n*=44 0.10 (NR)	*n*=49 2.0 (NR)	*n*=44 −1.8 (4.05)	*n*=49 0 (4.20)	*n*=44 −2.7 (5.11)	*n*=49 0.2 (5.25)	*n*=44 −1.2 (3.78)	*n*=49 −0.3 (3.92)
	Male	T2DM naive to oral AHGs	51.5	4-8	*n*=43 0.5 (NR)	*n*=38 0.3 (NR)	*n*=43 −1.0 (2.69)	*n*=38 0.3 (2.84)	*n*=43 −0.7 (5.31)	*n*=38 1.0 (5.55)	*n*=43 −2.2 (3.87)	*n*=38 −1.4 (4.07)

Abbreviations: *AHGs*, anti-hyperglycaemic drugs; *BMD*, bone mineral density; *mean ± SD*, mean and standard deviation; *mg*/d, milligram pear day; *NR*, not report; *T2DM*, type 2 diabetes mellitus; *TZD*, thiazolidinedione; *vs.*, versus.
Note: ‡ Mean age and dosages present for active TZDs drugs (pioglitazone or rosiglitazone); ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG.

2.7 Meta-analyses GRADE outcomes

2.7.1 TZDs fracture by severity and mechanism

Supplemental Table 2-16. GRADE evidence profile of TZDs fracture by severity and mechanism

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With TZDs		Risk with placebo / controls	Risk difference with TZDs
TZDs fracture by severity and mechanism (follow-up: range 12-261 weeks)											
86724 (45 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	847/44827 (1.9%)	1070/41897 (2.6%)	RR 1.36 (1.24 to 1.48)	2 per 100	1 more per 100 (from 0 fewer to 1 more)
Non-serious (follow-up: range 12-261 weeks)											
31329 (23 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	519/15872 (3.3%)	631/15457 (4.1%)	RR 1.33 (1.19 to 1.49)	3 per 100	1 more per 100 (1 more to 2 more)
Serious (follow-up: range 24-261 weeks)											
22959 (25 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⊕⊕◯◯ LOW	139/11512 (1.2%)	172/11447 (1.5%)	RR 1.30 (1.05 to 1.62)	1 per 100	0 fewer per 100 (0 fewer to 1 more)
Low-energy (follow-up: range 24-261 weeks)											
8564 (4 RCTs)	not serious	not serious	not serious	serious[d]	none	⊕⊕⊕◯ MODERATE	130/4999 (2.6%)	190/3565 (5.3%)	RR 1.51 (1.22 to 1.88)	3 per 100	1 more per 100 (1 more to 2 more)
High-energy (follow-up: range 24-162 weeks)											
6149 (6 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	35/2852 (1.2%)	50/3297 (1.5%)	RR 1.35 (0.89 to 2.05)	1 per 100	0 fewer per 100 (0 fewer to 1 more)
Stress (follow-up: median 261 weeks)											
3876 (1 RCT)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	8/1937 (0.4%)	10/1939 (0.5%)	RR 1.25 (0.49 to 3.16)	0 per 100	0 fewer per 100 (0 fewer to 1 more)
Pathological (follow-up: range 76-261 weeks)											
13847 (5 RCTs)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	16/7655 (0.2%)	17/6192 (0.3%)	RR 1.47 (0.77 to 2.80)	0 per 100	0 fewer per 100 (0 fewer to 0 fewer)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio; **TZD:** thiazolidinedione.

2.7.1.1 GRADE evidence

a. Studies that carried large (14.4% and 9.1%) and (12) small weight (4.4%, 0.9%, 0.2%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1%, 0.0% and 0.0%) for the overall (effect estimate) EE rated as a high risk of bias due to lack of blinding as an open-label design (13) studies out of (44), in which (5) studies were unpublished RCTs.

b. The overall imprecision was precise with a very very very strong significant effect difference in the level of evidence (P<0.00001). However, the studies reported an overlap CIs, except in 4 studies, in which (5) studies reported wide CIs. The 95% CI was consistent with a possibility for large harm exceeding a minimal important difference, including only (1,148) fracture events with large sample size.

c. The overall imprecision was precise with a significant effect difference (P=0.02). However, the studies reported an overlap CIs, in which (11) studies reported wide CIs. The 95% CI was not consistent with a possibility for harm exceeding a minimal important difference, including only (311) events with large sample size.

d. The overall imprecision was precise with a very very strong significant effect difference (P=0.0002). However, studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was not consistent with the possibility for harm exceeding a minimal important difference, including only (320) events with large sample size.

e. The overall imprecision was precise without significant of effect difference (P=0.16). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was not consistent with the possibility for harm exceeding a minimal important difference, including only (85) events with large sample size.

f. The overall imprecision was precise without significant of effect difference (P=0.64). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for harm exceeding a minimal important difference, including only (18) events with large sample size.

g. The overall imprecision was precise without significant of effect difference (P=0.24). However, studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for harm exceeding a minimal important difference, including only (33) events with large sample size.

In Summary, the overall certainty of the pooled EE was with moderate precise imprecision with a very very very strong effect level of evidence difference (P<0.00001). However, the majority of studies reported an overlap CIs, in which (18) reported wide CIs. The largest 3 studies did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of TZDs favour versus comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (1,915s) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.25; I^2=10%), or a subgroup difference across 6 studies (P=0.93; I^2=0%). Majority of studies at low risk of bias (70.2%). The overall magnitude of attrition and reporting bias were not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 13 studies with open-label design out of 44. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Although our population was restricted to people without a surgical intervention, however, our evidence may regard as indirect in relation to our broader question of interest. We were uncertain of the TZDs harm in T2DM patients with CAD, (2x2) factorial design, in which those participants were underwent for a surgical or therapeutic intervention. Finally, no evidence of reporting bias. However, (3) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

2.7.2 Pioglitazone fracture by treatment allocation

Supplemental Table 2-17. GRADE evidence profile of pioglitazone fracture by treatment allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by treatment allocation (follow-up: range 24-251 weeks)											
24718 (27 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	249/11991 (2.1%)	299/12727 (2.3%)	RR 1.19 (1.01 to 1.40)	2 per 100	0 fewer per 100 (0 fewer to 1 more)
Pioglitazone vs. placebo (follow-up: range 26-251 weeks)											
13451 (14 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ LOW	200/6184 (3.2%)	249/7267 (3.4%)	RR 1.21 (1.01 to 1.45)	3 per 100	1 more per 100 (0 fewer to 1 more)
Pioglitazone vs. controls (follow-up: range 24-251 weeks)											
11267 (13 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	49/5807 (0.8%)	50/5460 (0.9%)	RR 1.08 (0.73 to 1.59)	1 per 100	0 fewer per 100 (0 fewer to 0 fewer)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.2.1 GRADE evidence

a. Five studies that carried small weight (pioglitazone vs. placebo (7.1% and 0.2%) and (pioglitazone vs. control (2.8%, 0.4% and 0.3%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (27).

b. The overall imprecision was precise with a significant effect difference (P=0.04). However, all studies reported an overlap CIs, in which (5) studies reported wide CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (449) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.70). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (99) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with significant effect level of evidence difference (P=0.04). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (37%) and small studies (3.2% and 0.0%) did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (548) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.14; I^2=23%) or a subgroup difference (P=0.60; I^2=0%). Majority of studies at low risk of bias (89.2%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

2.7.3 Pioglitazone fracture by severity, mechanism and treatment allocation

Supplemental Table 2-18. GRADE evidence profile of pioglitazone fracture by severity, mechanism and treatment allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by severity, mechanism, and treatment allocation (placebo) (follow-up: range 24-251 weeks)											
39076 (14 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	417/18791 (2.2%)	576/20285 (2.8%)	RR 1.36 (1.20 to 1.53)	2 per 100	1 more per 100 (from 0 fewer to 1 more)
Non-serious											
10794 (7 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ LOW	181/5196 (3.5%)	230/5598 (4.1%)	RR 1.25 (1.03 to 1.51)	3 per 100	1 more per 100 (from 0 fewer to 2 more)
Serious											
6194 (7 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	66/2543 (2.6%)	103/3651 (2.8%)	RR 1.48 (1.10 to 1.98)	3 per 100	1 more per 100 (from 0 fewer to 3 more)
Low-energy											
3876 (1 RCT)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	119/1937 (6.1%)	178/1939 (9.2%)	RR 1.49 (1.20 to 1.87)	6 per 100	3 more per 100 (from 1 more to 5 more)
High-energy											
5066 (4 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	34/2530 (1.3%)	49/2536 (1.9%)	RR 1.43 (0.93 to 2.20)	1 per 100	1 more per 100 (from 0 fewer to 2 more)
Stress											
3876 (1 RCT)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	8/1937 (0.4%)	10/1939 (0.5%)	RR 1.25 (0.49 to 3.16)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Pathological											
9270 (3 RCTs)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	9/4648 (0.2%)	6/4622 (0.1%)	RR 0.67 (0.24 to 1.87)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Pioglitazone fracture by severity, mechanism, and treatment allocation (controls) (follow-up: range 24-251 weeks)											
11867 (13 RCTs)	serious[d]	not serious	not serious	very serious[h]	none	⊕◯◯◯ VERY LOW	49/6017 (0.8%)	50/5850 (0.9%)	RR 1.07 (0.73 to 1.56)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Non-serious											
4929 (6 RCTs)	serious[d]	not serious	not serious	very serious[i]	none	⊕◯◯◯ VERY LOW	30/2242 (1.3%)	41/2687 (1.5%)	RR 1.28 (0.81 to 2.01)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Serious											
6338 (7 RCTs)	serious[d]	not serious	not serious	very serious[j]	none	⊕◯◯◯ VERY LOW	18/3565 (0.5%)	9/2773 (0.3%)	RR 0.71 (0.32 to 1.55)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
High-energy											
600 (1 RCT)	not serious	not serious	not serious	very serious[k]	none	⊕⊕◯◯ LOW	1/210 (0.5%)	0/390 (0.0%)	RR 0.18 (0.01 to 4.40)	0 per 100	0 fewer per 100 (from 0 fewer to 2 more)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.3.1 GRADE evidence

a. Two studies that carried small weight (pioglitazone vs. placebo (4.2% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design.
b. The overall imprecision was precise with a significant effect difference (*P*=0.02). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (411) events with large sample size.
c. The overall imprecision was precise with a significant effect difference (*P*=0.010). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (169) events with large sample size.
d. The overall imprecision was precise with a very very significant effect difference (*P*=0.0004). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (297) events with large sample size.
e. The overall imprecision was precise without a significant effect difference (*P*=0.10). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (83) events with large sample size.
f. The overall imprecision was precise without a significant effect difference (*P*=0.64). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (18) events with large sample size.
g. The overall imprecision was precise without a significant effect difference (*P*=0.44). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (15) events with large sample size.
h. Three studies that carried small weight (pioglitazone vs. control (14.7%, 2.2% and 1.6%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design.
i. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.29). However, all studies reported an overlap CIs, in which (4) studies reported wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (71) events with large sample size.
j. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.38). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (27) events with large sample size.
k. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.29). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (1) event with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a very very very significant effect level of evidence difference (*P*<0.00001) in studies compared pioglitazone vs. placebo, but not with those vs. active comparators (*P*=0.75). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (28%) and small studies (1.9% and 0.1%) did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (1,092) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.26 and I^2=15% vs. placebo across 23 studies; vs. *P*=0.30 and I^2=14% active comparators across 14 studies) or subgroup difference (*P*=0.59 and I^2=0% vs. placebo across 6 studies; *P*=0.24 and I^2=30.3% vs. active comparators across 3 studies), FE model. However, the RE model predicts a significant magnitude difference across studies variance (T^2=0.02%). As such variation indicates that of a real differences in pioglitazone effect in each study as well as sampling variability due to chance, in which could be explained by differences in study populations (such as age of patients), interventions received (such as dose of drug), follow-up length, or other factors including stroke-related disability as a recurrent fall. Majority of studies at low risk of bias (95.7%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

2.7.4 Pioglitazone fracture by skeletal location and treatment allocation

Supplemental Table 2-19. GRADE evidence profile of pioglitazone fracture by skeletal location and treatment allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by skeletal location and treatment allocation follow-up: range 24 weeks to 251 weeks)											
59308 (16 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	168/30949 (0.5%)	274/28359 (1.0%)	RR 1.58 (1.32 to 1.91)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Spine pioglitazone vs. placebo (follow-up: range 150 weeks to 251 weeks)											
9777 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	19/4685 (0.4%)	44/5092 (0.9%)	RR 2.13 (1.28 to 3.55)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Spine pioglitazone vs. controls (follow-up: mean 78 weeks)											
2121 (1 RCT)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	1/1532 (0.1%)	0/589 (0.0%)	RR 0.87 (0.04 to 21.23)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Hip pioglitazone vs. placebo (follow-up: range 24 weeks to 78 weeks)											
9370 (3 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	25/4697 (0.5%)	35/4673 (0.7%)	RR 1.38 (0.84 to 2.28)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Hip pioglitazone vs. controls (follow-up: range 32 weeks to 251 weeks)											
2241 (2 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	1/1612 (0.1%)	1/629 (0.2%)	RR 1.10 (0.12 to 9.99)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Femur pioglitazone vs. placebo (follow-up: median 251 weeks)											
3876 (1 RCT)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	0/1937 (0.0%)	4/1939 (0.2%)	RR 8.99 (0.48 to 166.88)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Femur pioglitazone vs. controls (follow-up: range 32 weeks to 78 weeks)											
2638 (2 RCTs)	serious[a]	not serious	not serious	very serious[g]	none	⊕◯◯◯ VERY LOW	2/1793 (0.1%)	0/845 (0.0%)	RR 0.53 (0.06 to 4.79)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Upper-limbs pioglitazone vs. placebo (follow-up: range 150 weeks to 251 weeks)											
9114 (2 RCTs)	not serious	not serious	not serious	very serious[h]	none	⊕⊕◯◯ LOW	56/4570 (1.2%)	77/4544 (1.7%)	RR 1.37 (0.98 to 1.93)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Upper-limbs pioglitazone vs. controls (follow-up: range 54 weeks to 78 weeks)											
2158 (2 RCTs)	not serious	not serious	not serious	very serious[i]	none	⊕⊕◯◯ LOW	0/504 (0.0%)	2/1654 (0.1%)	RR 1.43 (0.18 to 11.54)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Distal upper-limbs (wrist) pioglitazone vs. placebo (follow-up: mean 126 weeks)											
602 (1 RCT)	not serious	not serious	not serious	very serious[j]	none	⊕⊕◯◯ LOW	0/299 (0.0%)	3/303 (1.0%)	RR 6.91 (0.36 to 133.16)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Distal upper-limbs (wrist) pioglitazone vs. controls (follow-up: range 24 weeks to 78 weeks)											
1143 (2 RCTs)	not serious	not serious	not serious	very serious[k]	none	⊕⊕◯◯ LOW	1/483 (0.2%)	2/660 (0.3%)	RR 1.23 (0.18 to 8.38)	0 per 100	0 fewer per 100 (from 0 fewer to 2 more)
Lower limbs pioglitazone vs. placebo (follow-up: range 88 weeks to 251 weeks)											
9264 (3 RCTs)	serious[a]	not serious	not serious	very serious[l]	none	⊕◯◯◯ VERY LOW	54/4643 (1.2%)	100/4621 (2.2%)	RR 1.85 (1.33 to 2.56)	1 per 100	1 more per 100 (from 0 fewer to 2 more)
Lower limbs pioglitazone vs. controls (follow-up: mean 78 weeks)											

Certainty assessment							Summary of findings				
2664 (2 RCTs)	serious[a]	not serious	not serious	very serious[m]	none	⊕◯◯◯ VERY LOW	1/1805 (0.1%)	2/859 (0.2%)	RR 2.43 (0.32 to 18.41)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Distal lower-limbs (ankle) pioglitazone vs. placebo (follow-up: range 44 weeks to 156 weeks)											
1717 (5 RCTs)	not serious	not serious	not serious	very serious[n]	none	⊕⊕◯◯ LOW	5/606 (0.8%)	4/1111 (0.4%)	RR 0.63 (0.21 to 1.90)	1 per 100	0 fewer per 100 (from 1 fewer to 1 more)
Distal lower-limbs (ankle) pioglitazone vs. controls (follow-up: range 56 weeks to 78 weeks)											
2623 (2 RCTs)	serious[a]	not serious	not serious	very serious[o]	none	⊕◯◯◯ VERY LOW	3/1783 (0.2%)	0/840 (0.0%)	RR 0.37 (0.05 to 2.94)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.4.1 GRADE evidence

a. Five studies that carried small weight ((spine 0.5%) (hip 0.5% and 0.3%), (femur 0.5%) (lower-limb 0.5% and 0.3%) and (ankle 0.5%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (16).

b. The overall imprecision was precise with a strong significant effect difference (P=0.004). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (63) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.93). However, a study reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (1) event with large sample size.

d. The overall imprecision was precise without a significant effect difference (P=0.20). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (60) events with large sample size.

e. The overall imprecision was precise without significant effect difference (P=0.93). However, all studies reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (2) events with large sample size.

f. The overall imprecision was precise without a significant effect difference (P=0.14). However, a study reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (4) events with large sample size.

g. The overall imprecision was precise without a significant effect difference (P=0.57). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (9) events with large sample size.

h. The overall imprecision was precise without a significant effect difference (P=0.07). However, all studies reported an overlap CIs and in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (133) events with large sample size.

i. The overall imprecision was precise without a significant effect difference (P=0.74). However, all studies reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (2) events with large sample size.

g. The overall imprecision was precise without a significant effect difference (P=0.20). However, a study reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (3) events with small sample size.

k. The overall imprecision was precise without a significant effect difference (P=0.83). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (3) events with small sample size.

l. The overall imprecision was precise with a very very significant effect difference (P=0.0002). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (154) events with large sample size.

m. The overall imprecision was precise without a significant effect difference (P=0.39). However, all studies reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (3) events with large sample size.

n. The overall imprecision was precise without a significant effect difference (P=0.41). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (9) events with small sample size.

o. The overall imprecision was precise without a significant effect difference (P=0.34). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (3) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a very very very significant effect level of evidence difference (P<0.00001). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (24.1%) did not cross the line of no difference (1), in which reports a significant association of lower-limbs fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (442) events in total with large sample size. Although, there was no evidence of inconsistency or a statistical important heterogeneity (P=0.70; I^2=0%). However, in a subgroup analysis, spinal fracture in pioglitazone vs. placebo, there was a moderate with a borderline nonsignificant evidence of heterogeneity across 31 studies (I^2=66%; P=0.05). No evidence of a subgroup difference across 14 studies (P=0.58; I^2=0%), FE model. However, the RE model predicts a significant magnitude difference across studies variance (T^2=0.00%). As such variation indicates that a real difference in pioglitazone effect in each study as well as sampling variability due to chance, in which could be explained by differences in study populations (such as age of patients), interventions received (such as dose of drug), follow-up length, or other factors including stroke-related disability as a recurrent fall. Majority of studies at low risk of bias (96.4%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 3 studies with open-label design out of 16. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

2.7.5 Pioglitazone fracture by gender and treatment allocation

Supplemental Table 2-20. GRADE evidence profile of pioglitazone fracture by gender and treatment allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by gender (follow-up: range 24-251 weeks)											
13464 (8 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	186/6656 (2.8%)	243/6808 (3.6%)	RR 1.31 (1.09 to 1.58)	3 per 100	1 more per 100 (0 fewer to 2 more)
Females (follow-up: range 24-251 weeks)											
5315 (8 RCTs)	not serious	not serious	not serious	very serious[a]	none	⊕⊕◯◯ LOW	89/2649 (3.4%)	133/2666 (5.0%)	RR 1.56 (1.20 to 2.02)	3 per 100	2 more per 100 (from 1 more to 3 more)
Females – pioglitazone vs. placebo (follow-up: range 78-251 weeks)											
3269 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	74/1675 (4.4%)	109/1594 (6.8%)	RR 1.56 (1.17 to 2.07)	4 per 100	2 more per 100 (from 1 more to 5 more)
Females – pioglitazone vs. controls (follow-up: range 24-144 weeks)											
2046 (5 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	15/974 (1.5%)	24/1072 (2.2%)	RR 1.55 (0.84 to 2.86)	2 per 100	1 more per 100 (from 0 fewer to 3 more)
Males (follow-up: range 24-251 weeks)											
8149 (6 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	97/4007 (2.4%)	110/4142 (2.7%)	RR 1.10 (0.84 to 1.43)	2 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Males – pioglitazone vs. placebo (follow-up: range 150-251 weeks)											
6001 (2 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	81/2973 (2.7%)	94/3028 (3.1%)	RR 1.13 (0.84 to 1.52)	3 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Males – pioglitazone vs. controls (follow-up: range 24-144 weeks)											
2148 (4 RCTs)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	16/1034 (1.5%)	16/1114 (1.4%)	RR 0.95 (0.49 to 1.82)	2 per 100	0 fewer per 100 (from 1 fewer to 1 more)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.5.1 GRADE evidence

a. The overall imprecision was precise and narrow CIs with a very very strong significant effect difference (P=0.0008). The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (222) events with large sample size.

b. The overall imprecision was precise with a very strong significant effect difference (P=0.002). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (183) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.16). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (39) events with large sample size.

d. The overall imprecision was precise and narrow CIs without a significant effect difference (P=0.49). The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (207) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.41). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (175) events with large sample size.

f. The overall imprecision was precise without a significant effect difference (P=0.87). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (32) events with large sample size.

In summary, the overall certainty of the pooled EE was with high precise imprecision with a very very significant effect level of evidence difference (P=0.0008) in studies compared pioglitazone vs. placebo and active comparators in females, but not in males (P=0.49). However, the majority of studies reported an overlap CIs, in which (4) reported wide CIs. The largest (52.5% and 25.5%) studies did not cross the line of no difference (1), in which reports a significant association of fracture in the direction of pioglitazone favour across placebo in females. However, the 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including (222 events in females vs. 207 events in males) in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.47 and I^2=0% in females vs. P=0.33 and I^2=14% in males) or subgroup

difference (P=0.99 and I^2=0% in females vs. P=0.62 and I^2=0% in males). All studies at low risk of bias (100%). The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

2.7.6 Pioglitazone fracture by bone mineral density and skeletal location

Supplemental Table 2-21. GRADE evidence profile of pioglitazone fracture by bone mineral density and skeletal allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone BMD by skeletal location (follow-up: range 52-126 weeks)											
851 (3 RCTs)	not serious	not serious	not serious	very serious[a]	none	⊕⊕◯◯ LOW	435	416	-	-	SMD 0.23 lower (0.36 lower to 0.09 lower)
Lumber spine (follow-up: range 52-126 weeks)											
646 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	331	315	-	-	SMD 0.18 lower (0.34 lower to 0.03 lower)
Hip (follow-up means 52 weeks)											
86 (1 RCT)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	43	43	-	-	SMD 0.53 lower (0.96 lower to 0.1 lower)
Femural neck (follow-up means 78 weeks)											
119 (1 RCT)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	61	58	-	-	SMD 0.25 lower (0.61 lower to 0.11 higher)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.6.1 GRADE evidence

a. The overall imprecision was precise and narrow with a significant effect difference (P=0.001). The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events with small sample size.

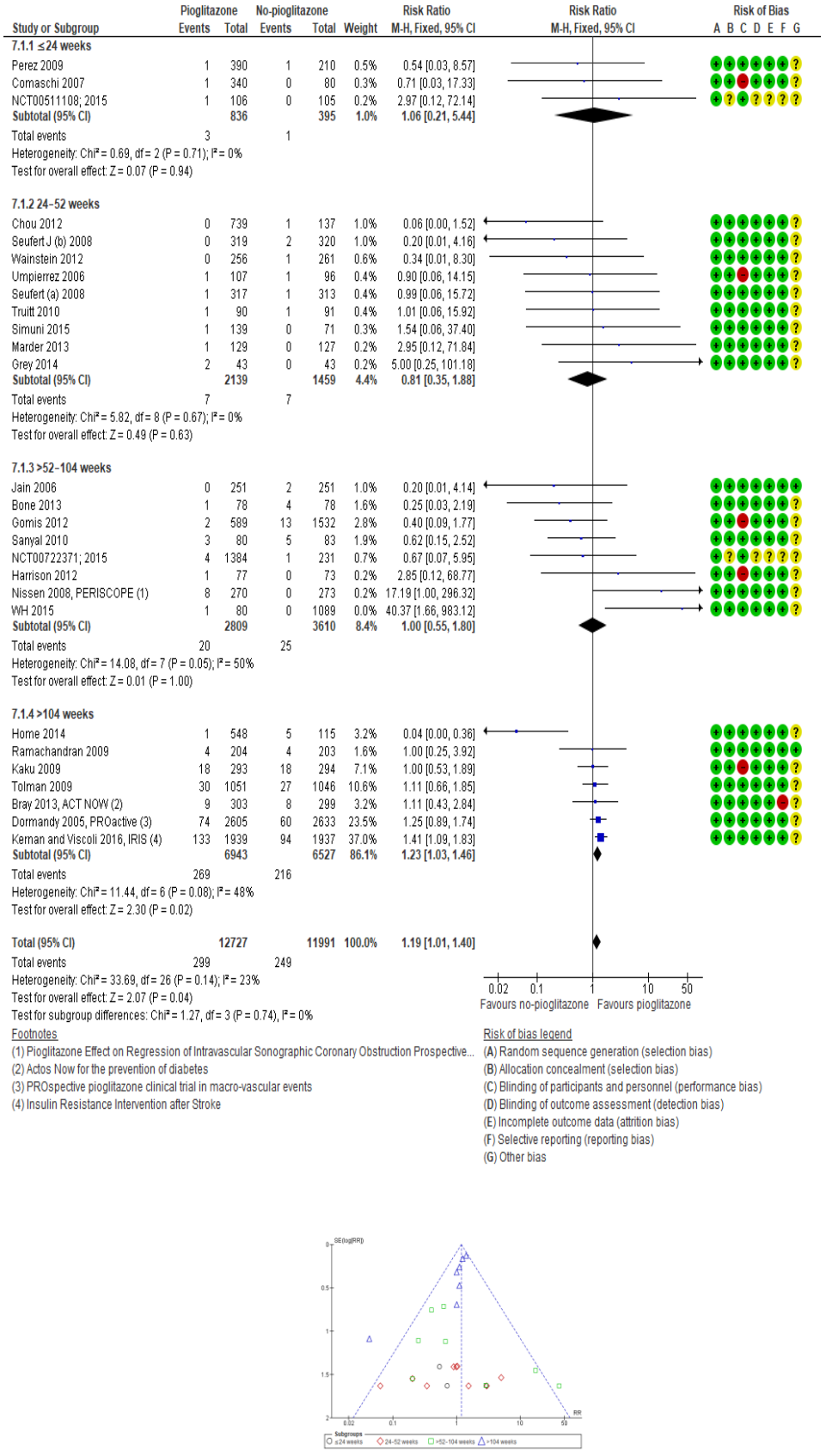
b. The overall imprecision was precise with a significant effect difference (P=0.02). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events with small sample size.

c. The overall imprecision was precise with a significant effect difference (P=0.02). However, included only one study which reported a significant reduction in hip BMD. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events with small sample size.

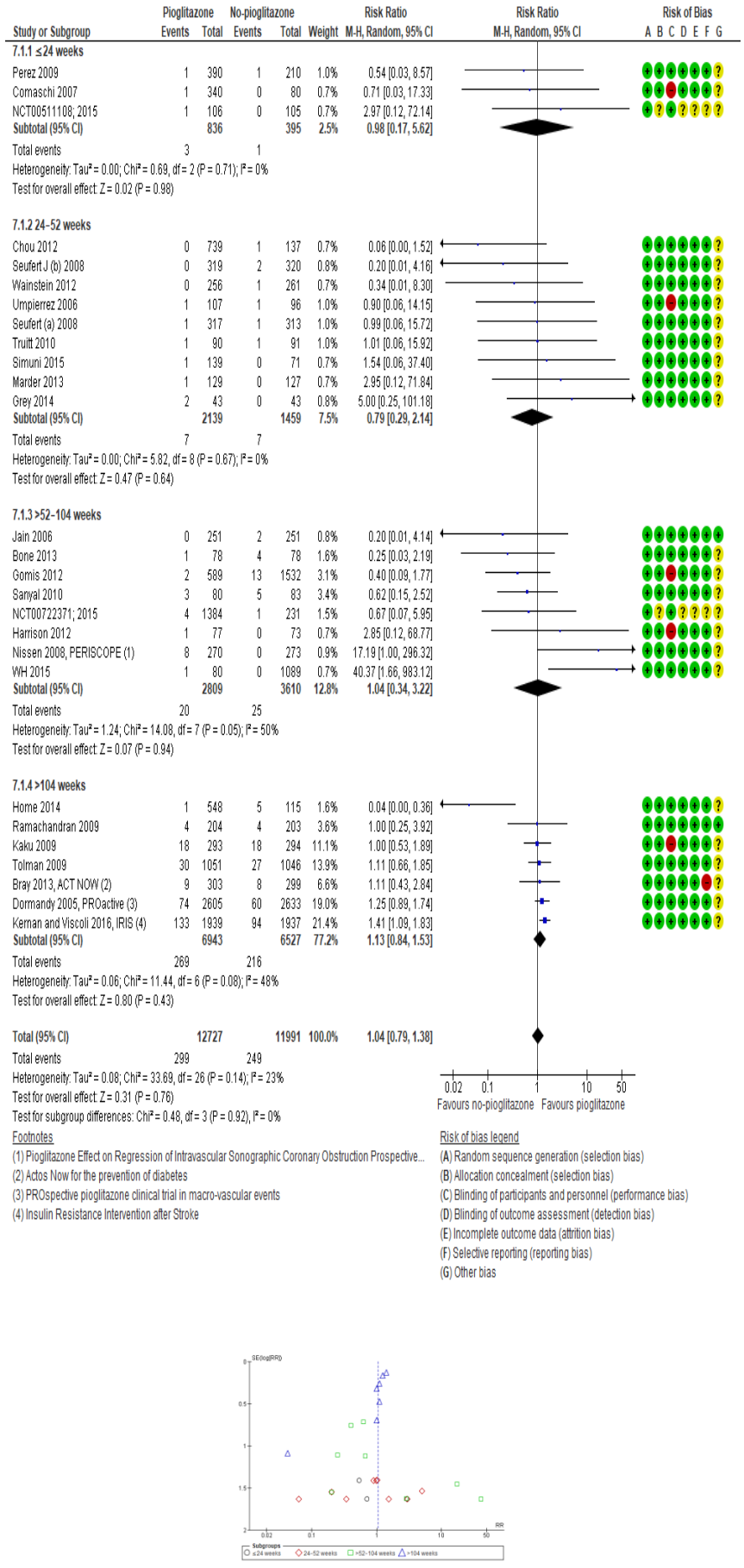
d. The overall imprecision was precise with a nonsignificant effect difference (P=0.17). However, included only one study with a narrow and overlap CIs, in which reported a nonsignificant reduction in femoral neck BMD. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events with small sample size.

In summary, the overall certainty of EE was with low precise imprecision with a very significant effect level of evidence difference (P=0.001). However, the majority of studies reported a small and overlap CIs. A small study (9.8%) did not cross the line of no difference (1) with a significant association of BMD loss in the direction of pioglitazone favour across comparators. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference with small sample size. No important heterogeneity or inconsistency of the pooled EE with (I^2=0%) without a significant statistically heterogeneity (P=0.52) or subgroup difference across 3 studies (I^2=9.8%; P=0.33), FE model. However, the RE model predicts a significant magnitude difference across studies variance (T^2=0.00%). As such variation indicates that a real difference in pioglitazone effect in each study as well as sampling variability due to chance, in which could be explained by differences in study populations (such as age of patients), interventions received (such as dose of drug), follow-up length, or other factors including stroke-related disability as a recurrent fall. All studies were at low risk of bias (100%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

2.7.7 Pioglitazone fracture by follow-up duration



Supplemental Figure 2-2. Forest and funnel plot of pioglitazone fracture by follow-up duration, Fixed-effect model.



Supplemental Figure 2-3. Forest and funnel plot of pioglitazone fracture by follow-up duration, Random-effect model.

Supplemental Table 2-22. GRADE evidence profile of pioglitazone fracture by follow-up duration

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture and follow-up duration (follow-up: range 24-251 weeks)											
24718 (27 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	249/11991 (2.1%)	299/12727 (2.3%)	RR 1.19 (1.01 to 1.40)	2 per 100	0 fewer per 100 (0 fewer to 1 more)
Follow-up duration-≤24 weeks											
1231 (3 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	1/395 (0.3%)	3/836 (0.4%)	RR 1.06 (0.21 to 5.44)	0 per 100	0 fewer per 100 (0 fewer to 1 more)
Follow-up duration-24–52 weeks											
3598 (9 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	7/1459 (0.5%)	7/2139 (0.3%)	RR 0.81 (0.35 to 1.88)	0 per 100	0 fewer per 100 (0 fewer to 0 fewer)
Follow-up duration->52–104 weeks											
6419 (8 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ VERY LOW	25/3610 (0.7%)	20/2809 (0.7%)	RR 1.00 (0.55 to 1.80)	1 per 100	0 fewer per 100 (0 fewer to 1 more)
Follow-up duration–>104 weeks											
13470 (7 RCTs)	serious[a]	not serious	not serious	serious[e]	none	⊕⊕◯◯ LOW	216/6527 (3.3%)	269/6943 (3.9%)	RR 1.23 (1.03 to 1.46)	3 per 100	1 more per 100 (0 fewer to 2 more)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.7.1 GRADE evidence

a. Five studies that carried small weight ((>104 weeks (7.1%), (>52-104 weeks (2.8% and 0.2%)), (≤24 weeks (0.3%) and (24-52 weeks (0.4%)) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (27).

b. The overall imprecision was precise without a significant effect difference (*P*=0.94). However, all studies reported overlap CIs, in which 2 studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (4) events with small sample size (1,231).

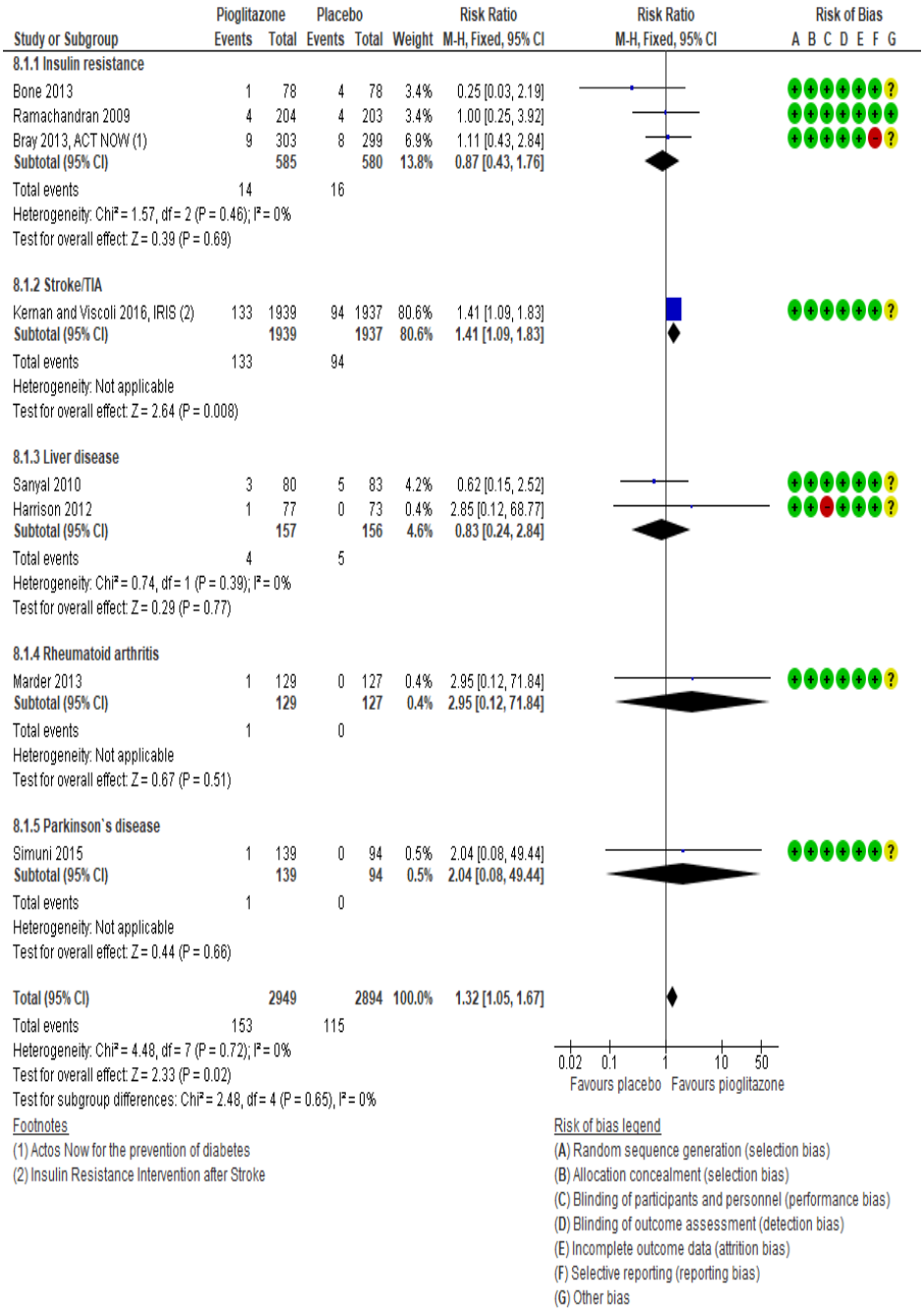
c. The overall imprecision was precise without a significant effect difference (*P*=0.63). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (14) events with large sample size.

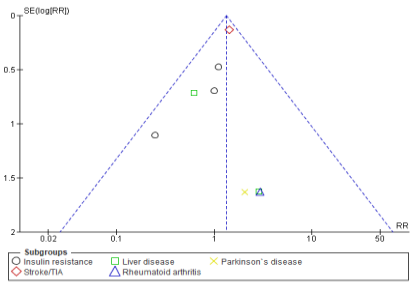
d. The overall imprecision was precise without a significant effect difference (*P*=1.00). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (45) events with large sample size.

e. The overall imprecision was precise with a significant effect difference (*P*=0.02). However, all studies reported a narrow and overlap CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (485) events with large sample size.

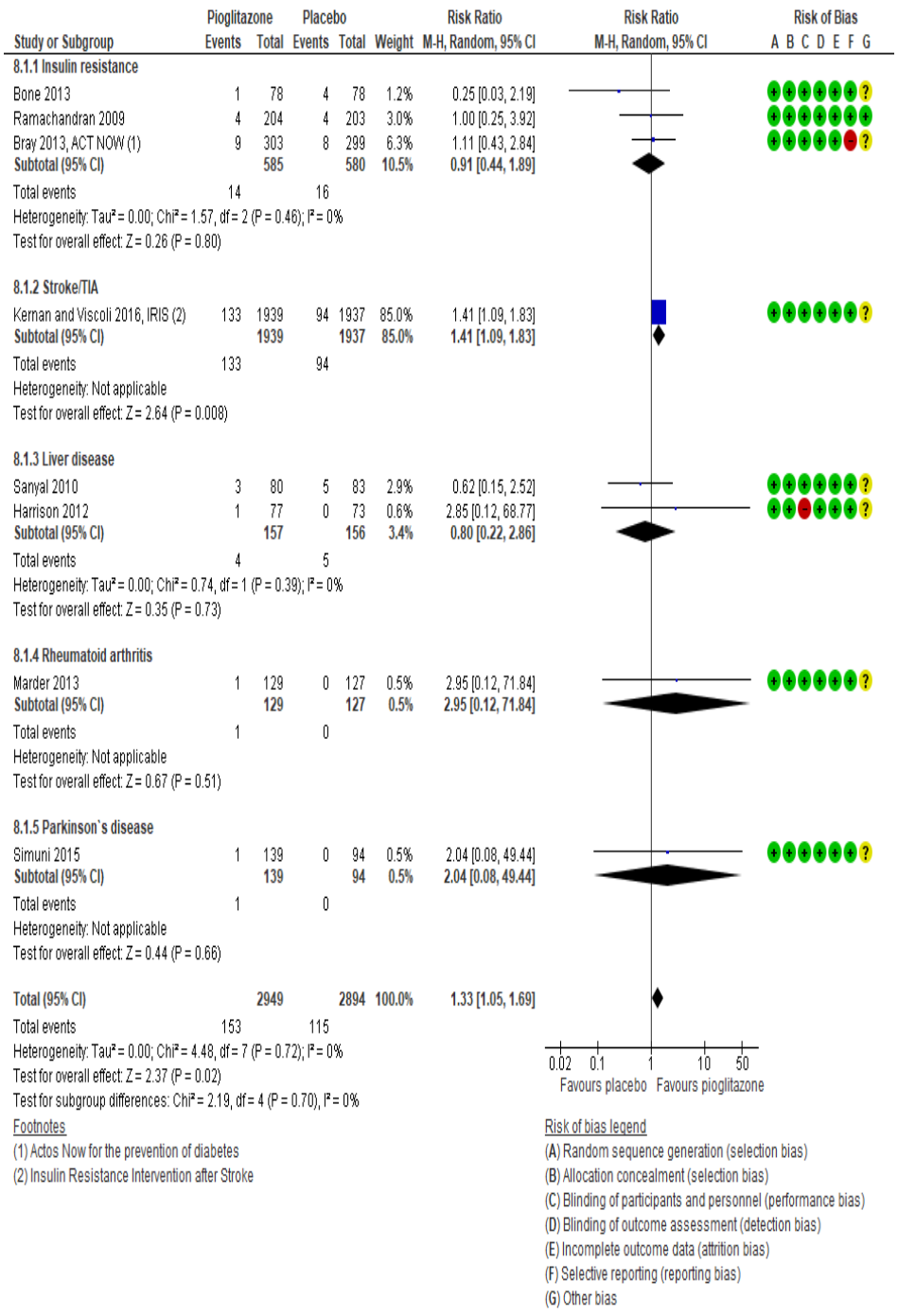
In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a significant effect level of evidence difference (*P*=0.04). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (37%) and small studies (3.2% and 0.0%) did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (548) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.14; I^2=23%) or subgroup difference (*P*=0.74; I^2=0%). Majority of studies at low risk of bias (89.2%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

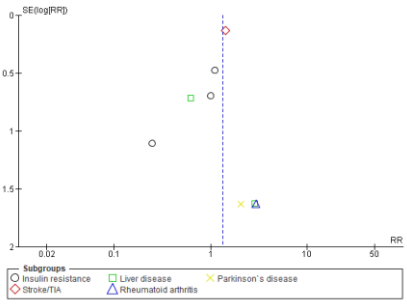
2.7.8 Pioglitazone fracture by baseline characteristics



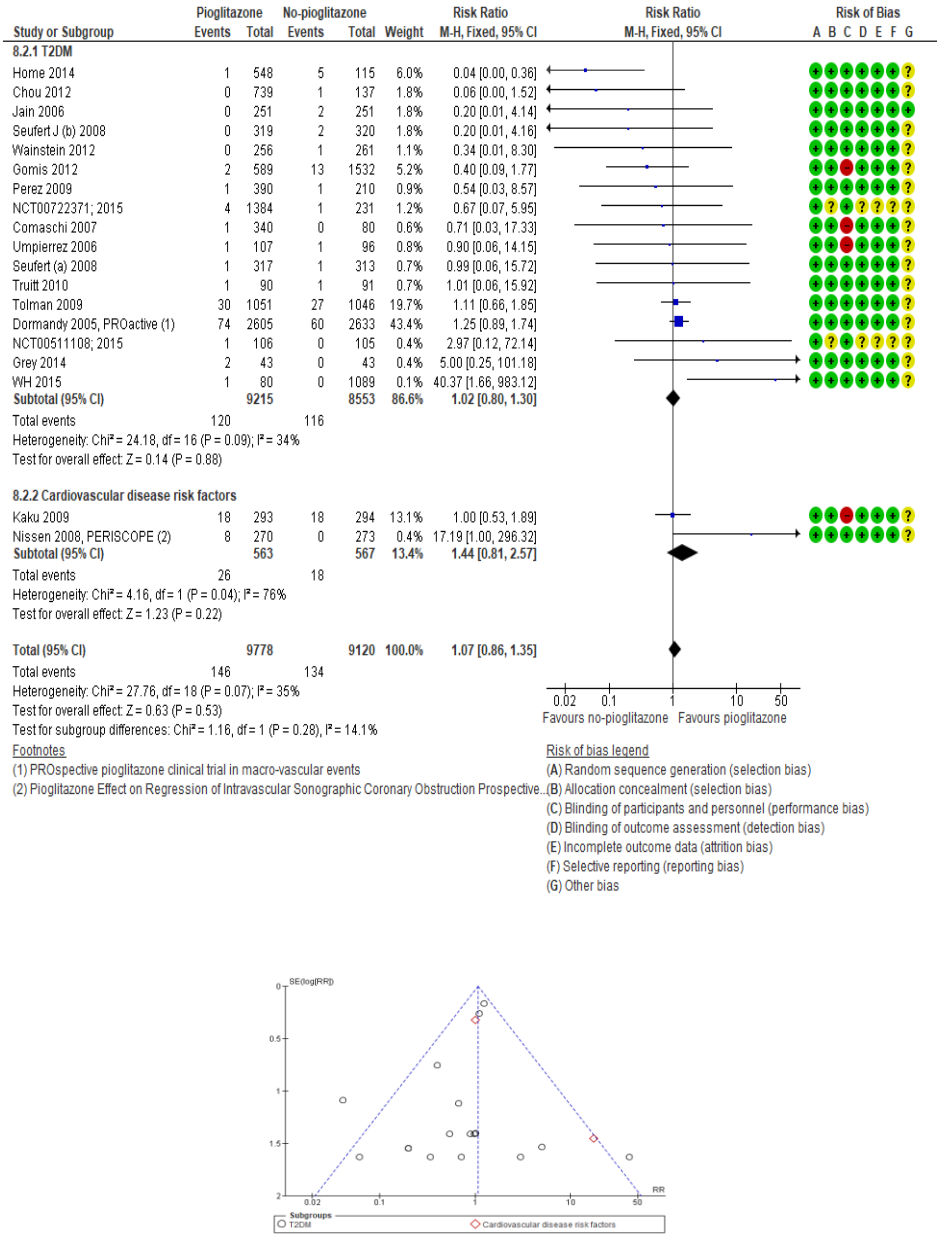


Supplemental Figure 2-4. Forest and funnel plot of pioglitazone fracture in insulin resistance individuals, Fixed-effect model.

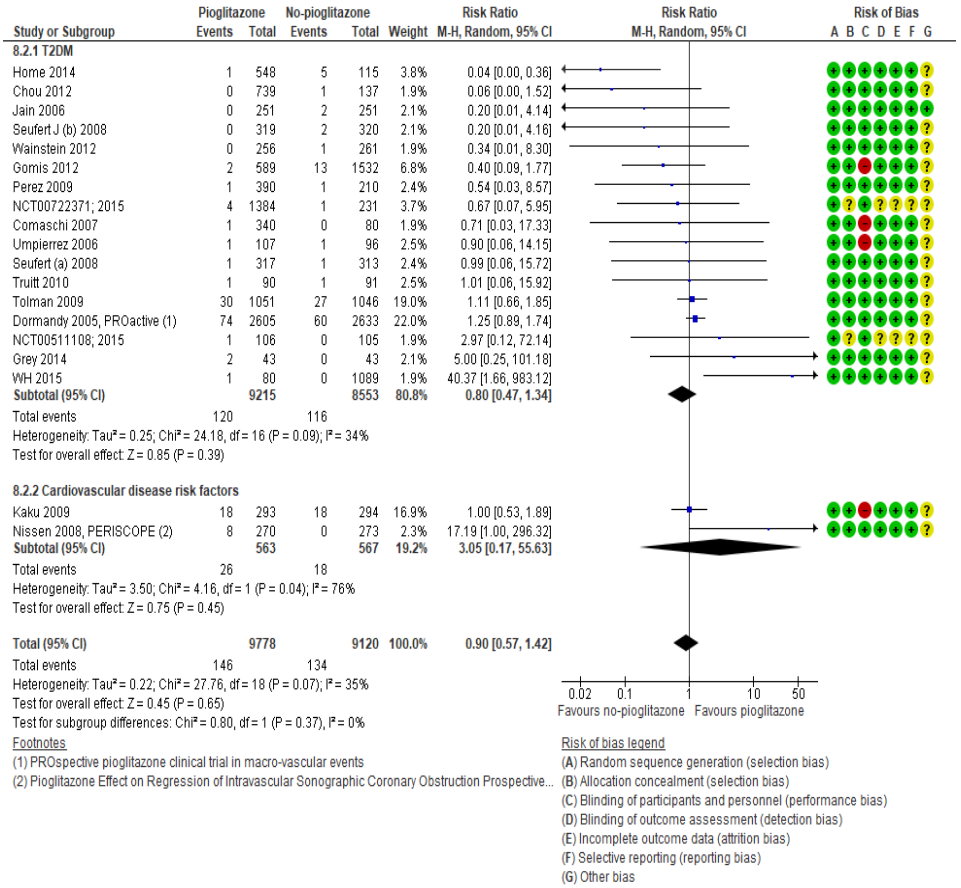


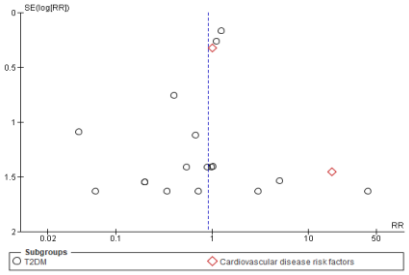


Supplemental Figure 2-5. Forest and funnel plot of pioglitazone fracture in insulin resistance individuals, Random-effect model.



Supplemental Figure 2-6. Forest and funnel plot of pioglitazone fracture in people with T2DM, Fixed-effect model.





Supplemental Figure 2-7. Forest and funnel plot of pioglitazone fracture in people with T2DM, Random-effect model.

Supplemental Table 2-23. GRADE evidence profile of pioglitazone fracture by baseline characteristics

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Nondiabetics (follow-up: range 24-251 weeks)											
5843 (8 RCTs)	serious[a]	not serious	not serious	very serious[a]	none	⊕◯◯◯ VERY LOW	115/2894 (4.0%)	153/2949 (5.2%)	RR 1.32 (1.05 to 1.67)	4 per 100	1 more per 100 (from 0 fewer to 3 more)
Insulin resistance (follow-up: range 78-157 weeks)											
1165 (3 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	16/580 (2.8%)	14/585 (2.4%)	RR 0.87 (0.43 to 1.76)	3 per 100	0 fewer per 100 (from 2 fewer to 2 more)
Stroke/TIA (follow-up: median 251 weeks)											
3876 (1 RCT)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	94/1937 (4.9%)	133/1939 (6.9%)	RR 1.41 (1.09 to 1.83)	5 per 100	2 more per 100 (from 0 fewer to 4 more)
Liver disease (follow-up: range 88-96 weeks)											
313 (2 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	5/156 (3.2%)	4/157 (2.5%)	RR 0.83 (0.24 to 2.84)	3 per 100	1 fewer per 100 (from 2 fewer to 6 more)
Rheumatoid arthritis (follow-up: range 24-251 weeks)											
256 (1 RCT)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	0/127 (0.0%)	1/129 (0.8%)	RR 2.95 (0.12 to 71.84)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Parkinson`s disease (follow-up: mean 44 weeks)											
233 (1 RCT)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	0/94 (0.0%)	1/139 (0.7%)	RR 2.04 (0.08 to 49.44)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Diabetics (follow-up: range 24-192 weeks)											
18898 (19 RCTs)	serious[h]	not serious	not serious	very serious[j]	none	⊕◯◯◯ VERY LOW	134/9120 (1.5%)	146/9778 (1.5%)	RR 1.07 (0.86 to 1.35)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
T2DM (follow-up: range 24-156 weeks)											
17768 (17 RCTs)	serious[h]	not serious	not serious	very serious[j]	none	⊕◯◯◯ VERY LOW	116/8553 (1.4%)	120/9215 (1.3%)	RR 1.02 (0.80 to 1.30)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Diabetics-cardiovascular disease risk factors (follow-up: range 78-192 weeks)											
1130 (2 RCTs)	serious[h]	not serious	not serious	very serious[k]	none	⊕◯◯◯ VERY LOW	18/567 (3.2%)	26/563 (4.6%)	RR 1.44 (0.81 to 2.57)	3 per 100	1 more per 100 (from 1 fewer to 5 more)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.8.1 GRADE evidence

a. A study that carried small weight (0.4%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (8) studies.

b. The overall imprecision was precise and narrow CIs with a significant effect difference (*P*=0.02). The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (268) events with large sample size.

c. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.69). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (30) events with small sample size.

d. The overall imprecision and narrow CIs was precise with a very significant effect difference (*P*=0.008). The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (227) events with large sample size.

e. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.77). However, all studies reported an overlap CIs, in which one study reported a wide CI. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (9) events with small sample size (313).

f. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.51). However, a study reported an overlap and wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (1) event with small sample size (256).

g. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.66). However, a study reported an overlap and wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (1) event with small sample size (233).

h. A study that carried large (13.1%) and small weight (5.2%, 0.8% and 0.6%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (19) studies.

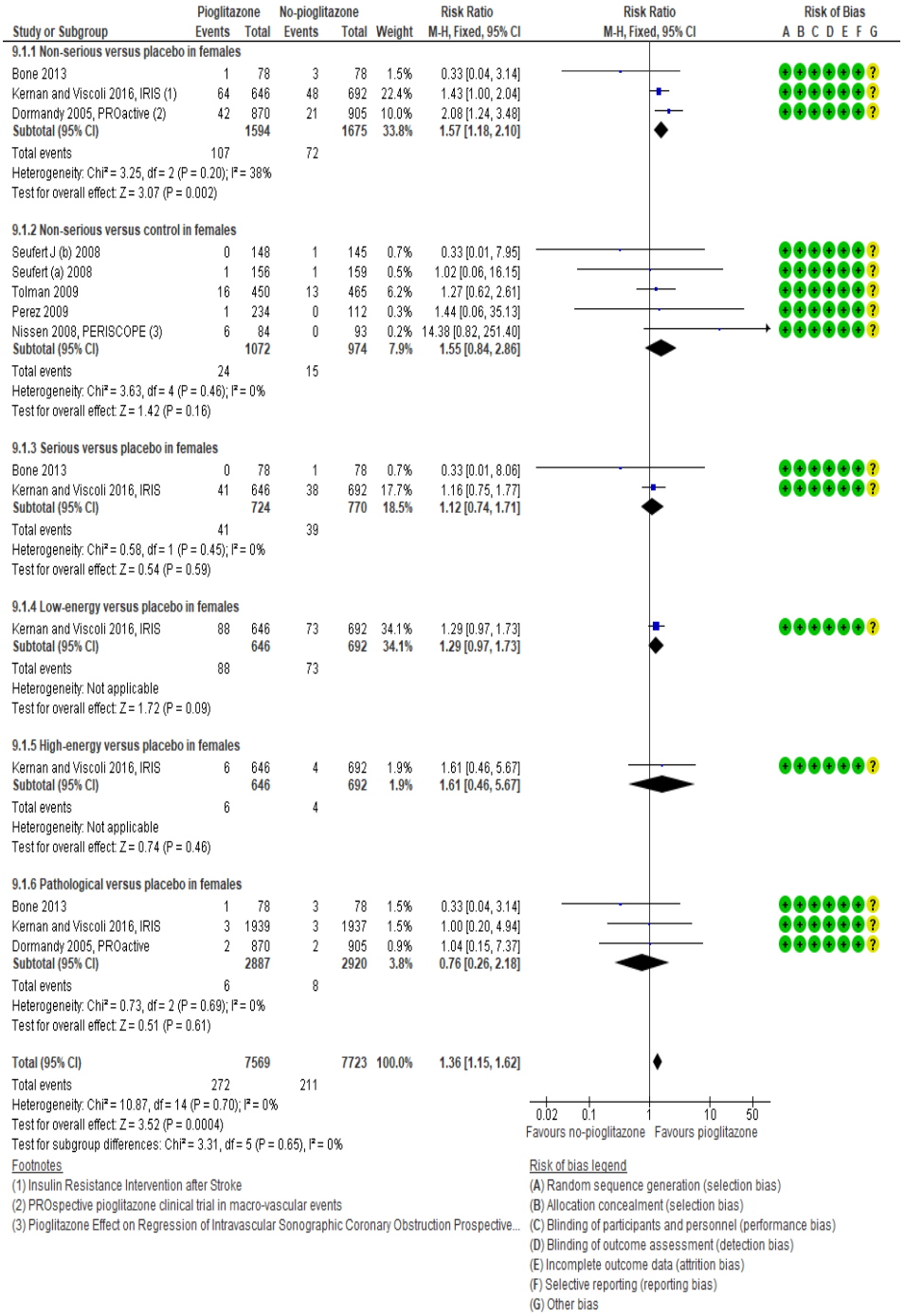
i. The overall imprecision was precise and narrow CIs without a significant effect difference (*P*=0.53). The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (280) events with large sample size.

j. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.88). However, all studies reported an overlap CIs, in which 7 studies reported wide CIs. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (236) events with large sample size.

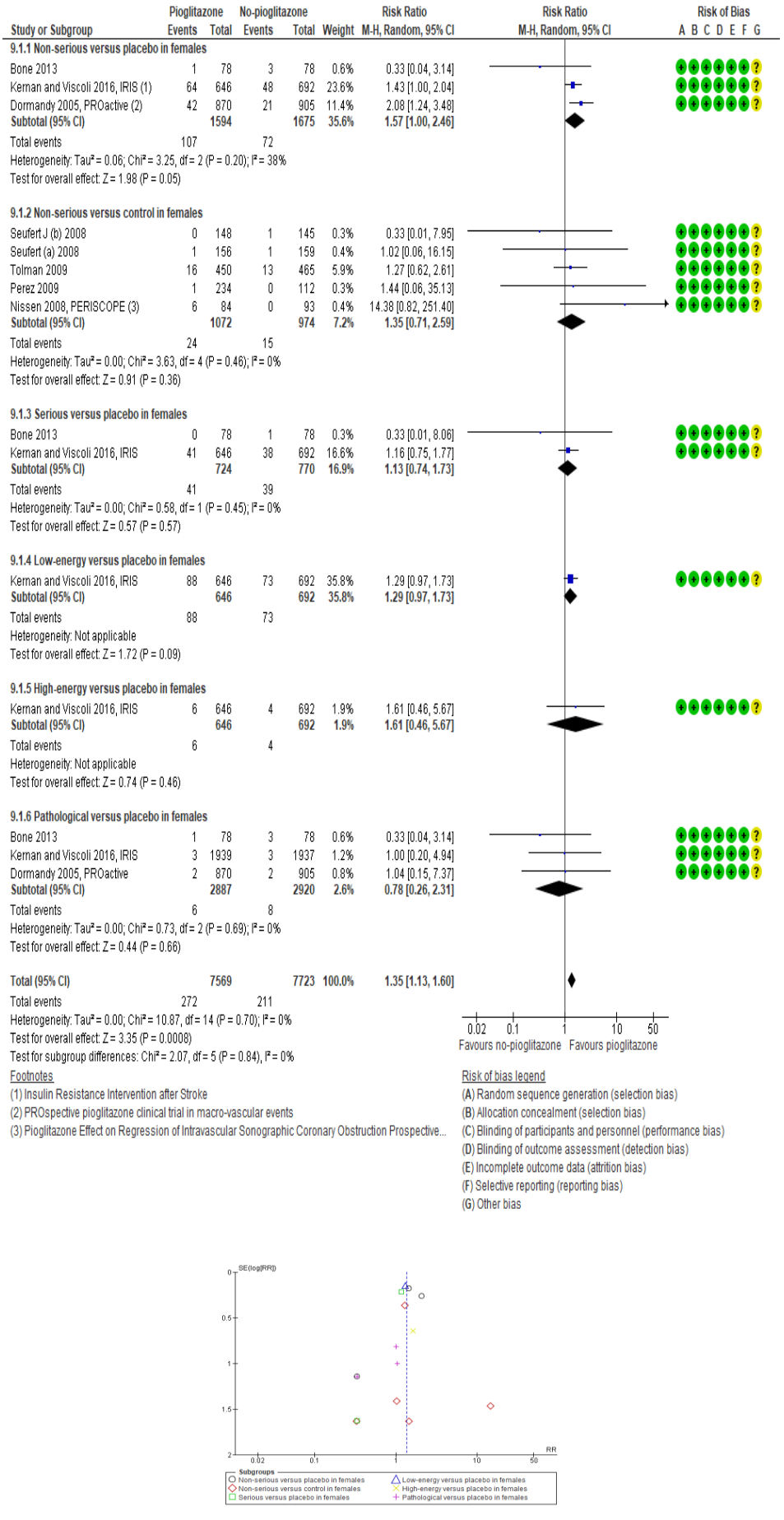
k. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.22). However, all studies reported an overlap CIs, in which one study reported a wide CI. The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (44) events with small sample size.

In summary, the overall certainty of the pooled EE was with very low precise imprecision with a significant effect level of evidence difference (*P*=0.02) in nondiabetics individuals, but not in people with diabetes (*P*=0.65). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. Three studies did not cross the line of no difference (1), in which a large study (80.6% in nondiabetic individuals) and small study (0.1%, in people with T2DM) reports a significant association of fracture in the direction of pioglitazone favour across comparators in people with T2DM. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (548) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.72 and I^2=0% vs. nondiabetic; and *P*=0.07 and I^2=35% vs. people with T2DM) or subgroup difference (*P*=0.65 and I^2=0% vs. nondiabetic; *P*=0.28 and I^2=14.1% vs. people with T2DM). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies in people with T2DM reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

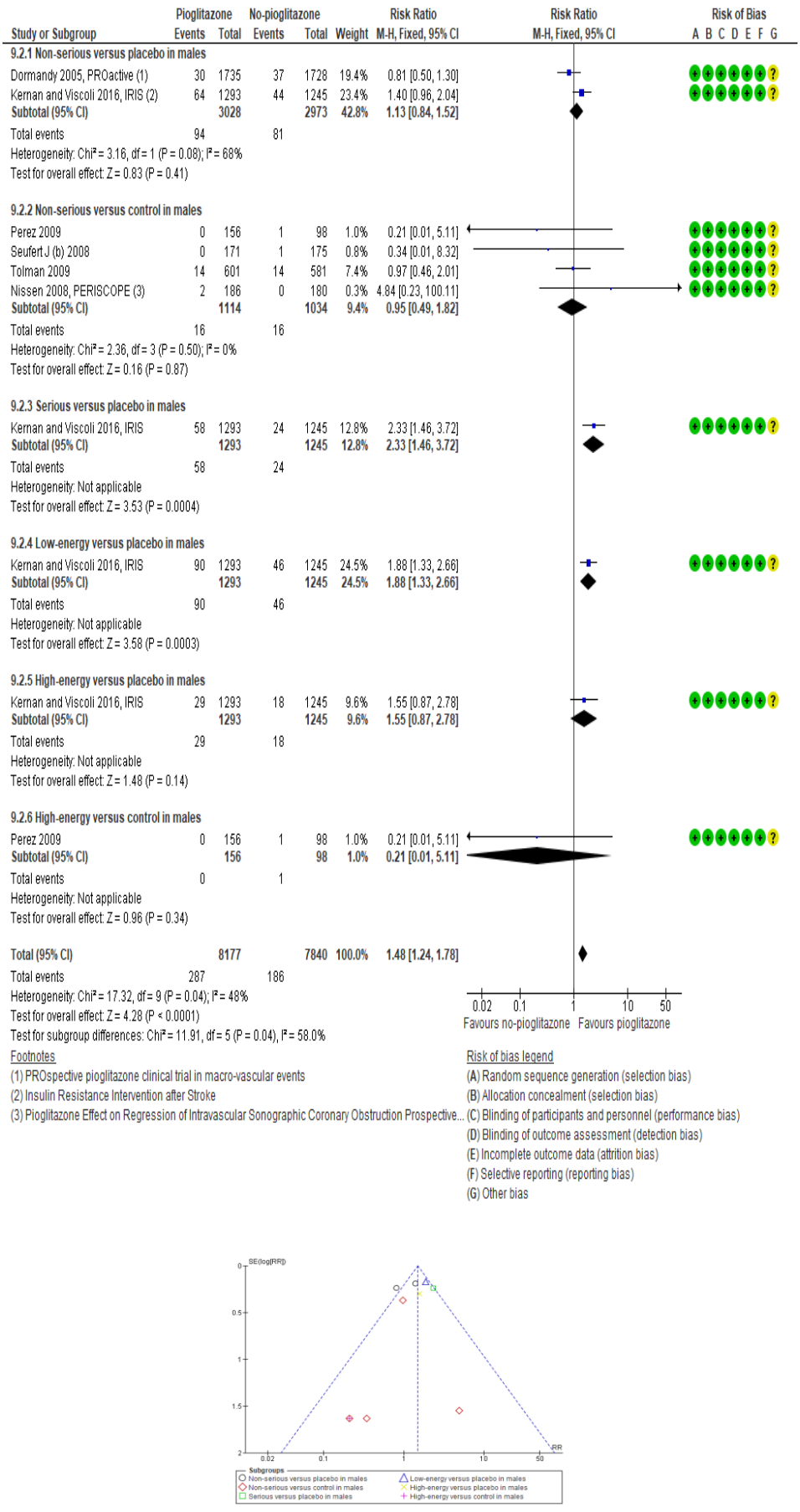
2.7.9 Pioglitazone fracture by gender, treatment allocation, severity and mechanism



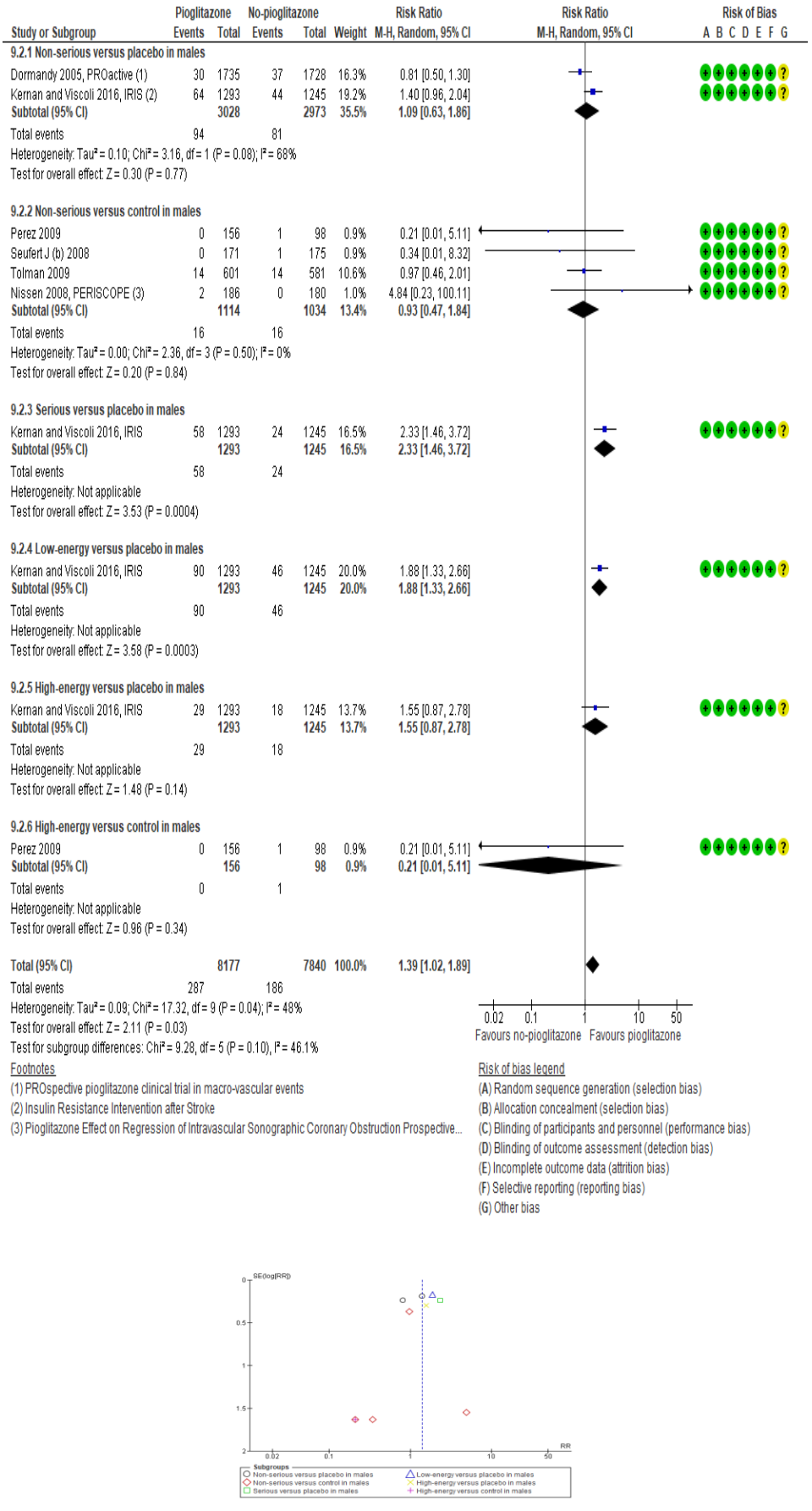
Supplemental Figure 2-8. Forest and funnel plot of pioglitazone fracture in females by treatment allocation, severity and mechanism, Fixed-effect model.



Supplemental Figure 2-9. Forest and funnel plot of pioglitazone fracture in females by treatment allocation, severity and mechanism, Random-effect model.



Supplemental Figure 2-10. Forest and funnel plot of pioglitazone fracture in males by treatment allocation, severity and mechanism, Fixed-effect model.



Supplemental Figure 2-11. Forest and funnel plot of pioglitazone fracture in males by treatment allocation, severity and mechanism, Random-effect model.

Supplemental Table 2-24. GRADE evidence profile of pioglitazone fracture by gender, treatment allocation, severity and mechanism

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by severity, mechanism, and treatment allocation in females (follow-up: range 24-251 weeks)											
21099 (8 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	219/10643 (2.1%)	278/10456 (2.7%)	RR 1.34 (1.13 to 1.59)	2 per 100	1 more per 100 (from 0 fewer to 1 more)
Non-serious pioglitazone vs. placebo (follow-up: range 87-251 weeks)											
3269 (3 RCTs)	not serious	not serious	not serious	very serious[a]	none	⊕⊕◯◯ LOW	72/1675 (4.3%)	107/1594 (6.7%)	RR 1.57 (1.18 to 2.10)	4 per 100	2 more per 100 (from 1 more to 5 more)
Non-serious pioglitazone vs. controls (follow-up: range 24-144 weeks)											
2046 (5 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	15/974 (1.5%)	24/1072 (2.2%)	RR 1.55 (0.84 to 2.86)	2 per 100	1 more per 100 (from 0 fewer to 3 more)
Serious pioglitazone vs. placebo (follow-up: range 78-251 weeks)											
1494 (2 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	39/770 (5.1%)	41/724 (5.7%)	RR 1.12 (0.74 to 1.71)	5 per 100	1 more per 100 (from 1 fewer to 4 more)
Low-energy pioglitazone vs. placebo (follow-up: median 251 weeks)											
1338 (1 RCT)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	73/692 (10.5%)	88/646 (13.6%)	RR 1.29 (0.97 to 1.73)	11 per 100	3 more per 100 (from 0 fewer to 8 more)
High-energy pioglitazone vs. placebo (follow-up: median 251 weeks)											
1338 (1 RCT)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	4/692 (0.6%)	6/646 (0.9%)	RR 1.61 (0.46 to 5.67)	1 per 100	0 fewer per 100 (from 0 fewer to 3 more)
Pathological pioglitazone vs. placebo (follow-up: range 78-251 weeks)											
5807 (3 RCTs)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	8/2920 (0.3%)	6/2887 (0.2%)	RR 0.76 (0.26 to 2.18)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Pioglitazone fracture by severity, mechanism, and treatment allocation in males (follow-up: range 24-251 weeks)											
16017 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	186/7840 (2.4%)	287/8177 (3.5%)	RR 1.48 (1.24 to 1.78)	2 per 100	1 more per 100 (from 1 more to 2 more)
Non-serious pioglitazone vs. placebo											
6001 (2 RCTs)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	81/2973 (2.7%)	94/3028 (3.1%)	RR 1.13 (0.84 to 1.52)	3 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Non-serious pioglitazone vs. controls											
2148 (4 RCTs)	not serious	not serious	not serious	very serious[h]	none	⊕⊕◯◯ LOW	16/1034 (1.5%)	16/1114 (1.4%)	RR 0.95 (0.49 to 1.82)	2 per 100	0 fewer per 100 (from 1 fewer to 1 more)
Serious pioglitazone vs. placebo											
2538 (1 RCT)	not serious	not serious	not serious	very serious[i]	none	⊕⊕◯◯ LOW	24/1245 (1.9%)	58/1293 (4.5%)	RR 2.33 (1.46 to 3.72)	2 per 100	3 more per 100 (from 1 more to 5 more)
Low-energy pioglitazone vs. placebo											
2538 (1 RCT)	not serious	not serious	not serious	very serious[j]	none	⊕⊕◯◯ LOW	46/1245 (3.7%)	90/1293 (7.0%)	RR 1.88 (1.33 to 2.66)	4 per 100	3 more per 100 (from 1 more to 6 more)
High-energy pioglitazone vs. placebo											
2538 (1 RCT)	not serious	not serious	not serious	very serious[k]	none	⊕⊕◯◯ LOW	18/1245 (1.4%)	29/1293 (2.2%)	RR 1.55 (0.87 to 2.78)	1 per 100	1 more per 100 (from 0 fewer to 3 more)
High-energy pioglitazone vs. controls											

Certainty assessment							Summary of findings				
254 (1 RCT)	not serious	not serious	not serious	very serious[l]	none	⊕⊕◯◯ LOW	1/98 (1.0%)	0/156 (0.0%)	RR 0.21 (0.01 to 5.11)	1 per 100	1 fewer per 100 (from 1 fewer to 4 more)

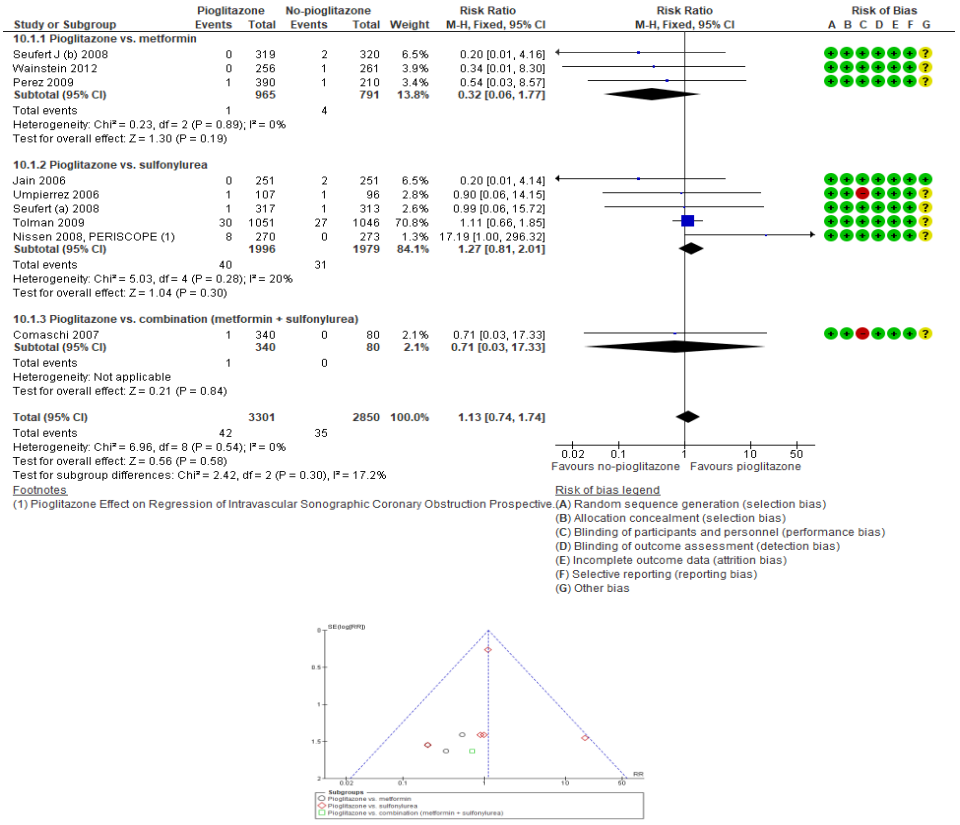
Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.9.1 GRADE evidence

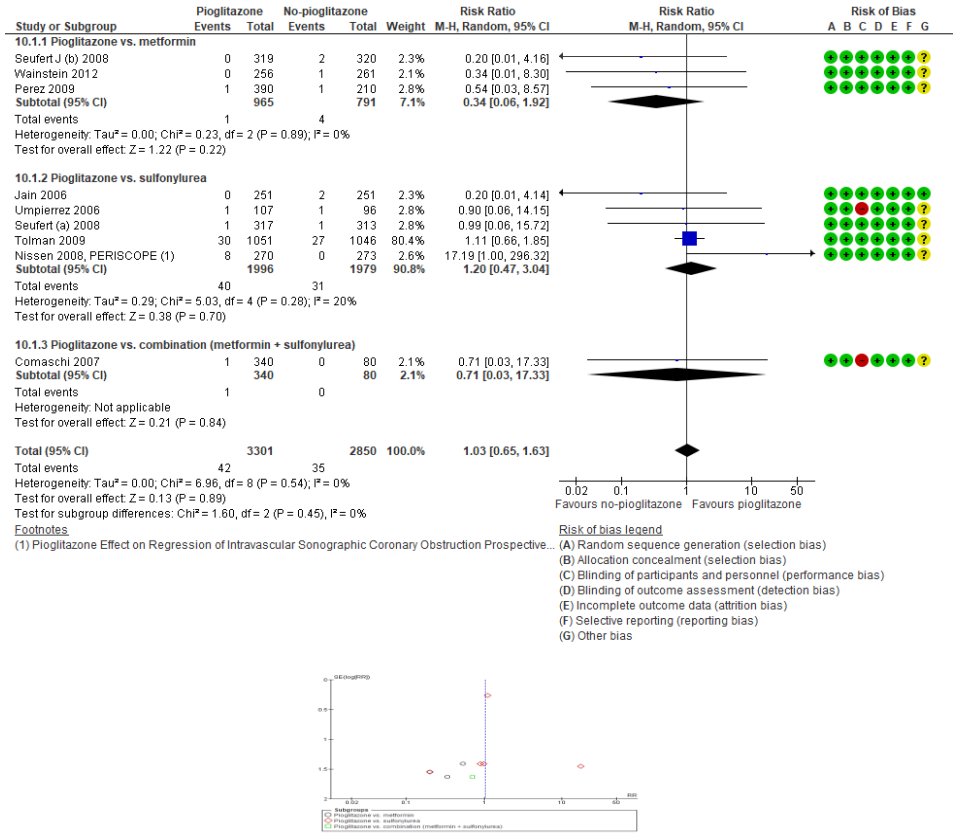
a. The overall imprecision was precise with a very strong significant effect difference (*P*=0.002). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (179) events with large sample size.
b. The overall imprecision was precise without a significant effect difference (*P*=0.16). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (39) events with large sample size.
c. The overall imprecision was precise without a significant effect difference (*P*=0.59). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (80) events with small sample size (1,494).
d. The overall imprecision was precise without a significant effect difference (*P*=0.09). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (161) events with large sample size.
e. The overall imprecision was precise without a significant effect difference (*P*=0.46). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (10) events with large sample size.
f. The overall imprecision was precise without a significant effect difference (*P*=0.61). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (14) events with large sample size.
g. The overall imprecision was precise without a significant effect difference (*P*=0.41). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (175) events with large sample size.
h. The overall imprecision was precise without a significant effect difference (*P*=0.87). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (32) events with large sample size.
i. The overall imprecision was precise with a very very significant effect difference (*P*=0.0004). However, all study reported a non-overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (82) events with large sample size.
j. The overall imprecision was precise with a very very significant effect difference (*P*=0.0003). However, all study reported a non-overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (106) events with large sample size.
k. The overall imprecision was precise without a significant effect difference (*P*=0.14). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (47) events with large sample size.
l. The overall imprecision was precise without a significant effect difference (*P*=0.34). However, all studies reported an overlap and narrow CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (1) event with small sample size.

In summary, the overall certainty of the pooled EE was with high precise imprecision with a very very significant effect level of evidence difference (*P*=0.0004) in studies compared pioglitazone vs. placebo and active comparators in females and in males (*P*<0.0001). However, the majority of studies reported an overlap CIs, in which (4) reported wide CIs. The largest study in males (24.5%) and large (22.4%) and small (10.0%) one in females did not cross the line of no difference (1), in which reports a significant association of fracture in the direction of pioglitazone favour across placebo in both genders. However, the 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (483 events in females vs. 473 events in males) in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.70 and I^2=0%) or subgroup difference (*P*=0.65 and I^2=0%) in females. In males, however, although the I^2 for the statistical heterogeneity (48%) or subgroup difference (58%) were not scored high, but there was an evidence of important inconsistency across 10 studies and subgroup difference across 6 studies (*P*=0.04), FE model. However, the RE model was not predicts a significant magnitude difference across studies variance (T^2=0.09%) without studies subgroups difference. As such variation indicates that a real difference in pioglitazone effect in each study as well as sampling variability due to chance, in which could be explained by differences in study populations (such as age of patients), interventions received (such as dose of drug), follow-up length, or other factors including stroke-related disability as a recurrent fall (IRIS trials dominator). All studies at low risk of bias (100%). The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, one study in males reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

2.7.10 Pioglitazone fracture vs. AHGs agents



Supplemental Figure 2-12. Forest and funnel plot of pioglitazone fracture versus AHGs agents, Fixed-effect model.



Supplemental Figure 2-13. Forest and funnel plot of pioglitazone fracture versus AHGs agents, Random-effect model.

Supplemental Table 2-25. GRADE evidence profile of pioglitazone fracture vs. AHGs agents

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With AHGs agents	With Pioglitazone		Risk with placebo	Risk difference with pioglitazone
Pioglitazone vs. AHG agents (follow-up: range 24-144 weeks)											
6151 (9 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	35/2850 (1.2%)	42/3301 (1.3%)	RR 1.13 (0.74 to 1.74)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Pioglitazone vs. metformin (follow-up: range 24-52 weeks)											
1756 (3 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	4/791 (0.5%)	1/965 (0.1%)	RR 0.32 (0.06 to 1.77)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Pioglitazone vs. sulfonylurea (follow-up: range 28-144 weeks)											
3975 (5 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ VERY LOW	31/1979 (1.6%)	40/1996 (2.0%)	RR 1.27 (0.81 to 2.01)	2 per 100	0 fewer per 100 (from 0 fewer to 2 more)
Pioglitazone vs. combination (metformin + sulfonylurea) (follow-up: mean 24 weeks)											
420 (1 RCT)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	0/80 (0.0%)	1/340 (0.3%)	RR 0.71 (0.03 to 17.33)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.10.1 GRADE evidence

a. Two studies that carried small weight (pioglitazone vs sulfonylurea (2.8%), (pioglitazone vs. metformin + sulfonylurea (2.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (9).

b. The overall imprecision was precise and narrow CIs without a significant effect difference (*P*=0.58). The 95% CI was consistent with the possibility for small harm not exceeding a minimal important difference, including only (77) events with large sample size.

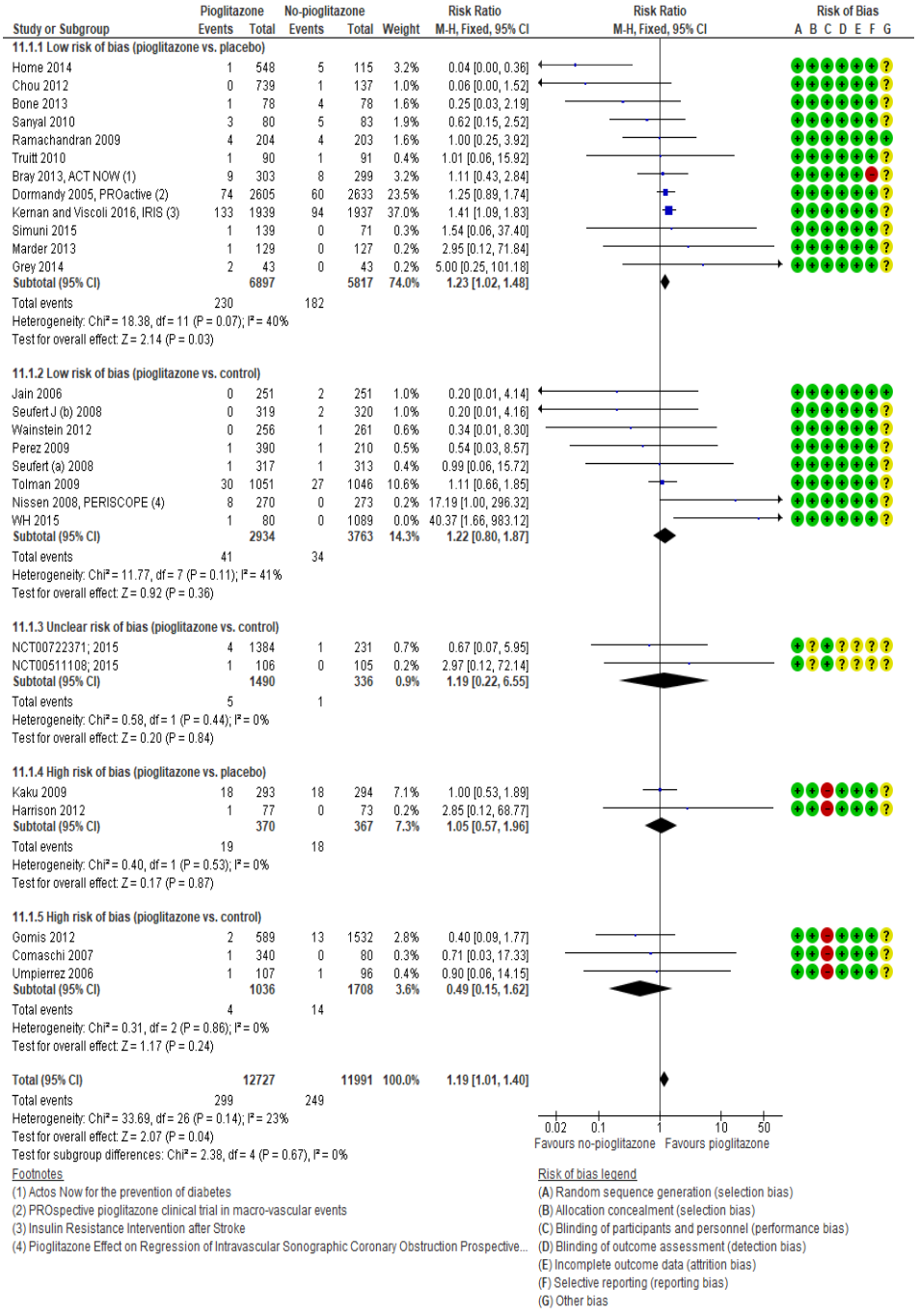
c. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.19). However, all studies reported an overlap CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events (5) with small sample size (1,756).

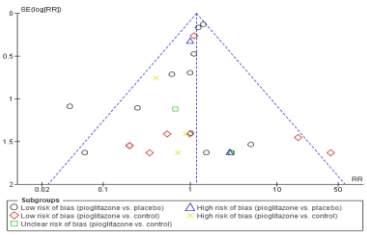
d. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.30). However, all studies reported an overlap CIs, in which 3 studies reported wide CIs and other one reported very-wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few events (71) with large sample size.

e. The overall imprecision was precise with a nonsignificant effect difference (*P*=0.84). However, one study reported an overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including few event (1) with small sample size (420).

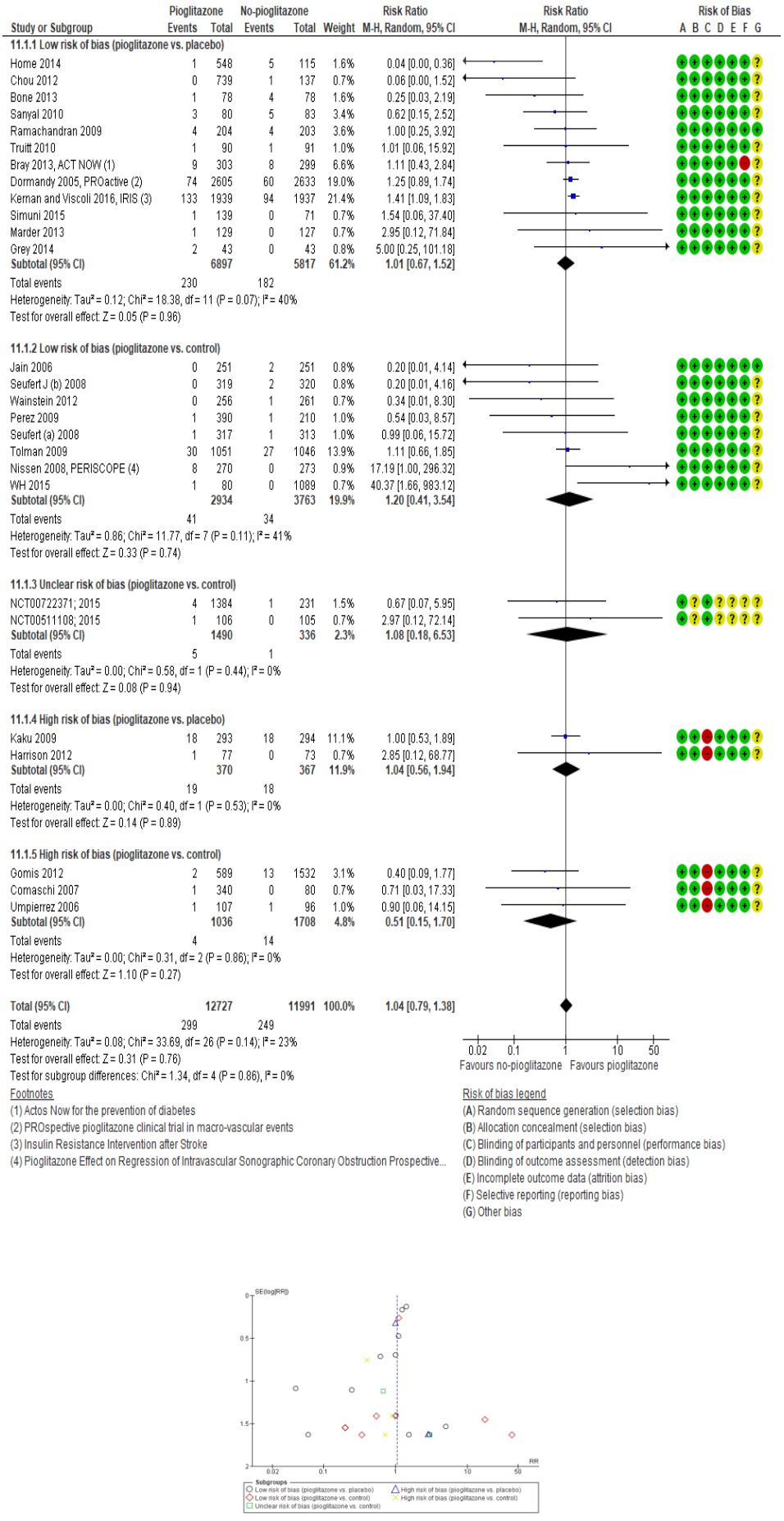
In summary, the overall certainty of the pooled EE was with very low precise imprecision without significant effect level of evidence difference (*P*=0.58). However, the majority of studies reported an overlap CIs and (4) reported wide CIs. One study not cross the line of no difference (1), in which reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including (77) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.54; I^2=0%) or subgroup difference (*P*=0.30; I^2=17.2%). Majority of studies at low risk of bias (95.1%). However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 2 studies with open-label design out of 9. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

2.7.11 Pioglitazone fracture by risk of bias and treatment allocation





Supplemental Figure 2-14. Forest and funnel plot of pioglitazone fracture by risk of bias and treatment allocation, Fixed-effect model.



Supplemental Figure 2-15. Forest and funnel plot of pioglitazone fracture by risk of bias and treatment allocation, Random-effect model.

Supplemental Table 2-26. GRADE evidence profile of pioglitazone fracture by risk of bias and treatment allocation

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by risk of bias and treatment allocation (follow-up: range 24-251 weeks)											
24718 (27 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	250/11991 (2.1%)	300/12727 (2.4%)	RR 1.18 (1.00 to 1.39)	2 per 100	0 fewer per 100 (0 fewer to 1 more)
Low risk of bias (pioglitazone vs. placebo) (follow-up: range 26-251 weeks)											
12714 (12 RCTs)	not serious	not serious	not serious	serious[b]	none	⊕⊕⊕◯ MODERATE	183/5817 (3.1%)	231/6897 (3.3%)	RR 1.22 (1.01 to 1.47)	3 per 100	1 more per 100 (0 fewer to 1 more)
Low-risk of bias (pioglitazone vs. control) (follow-up: range 24-144 weeks)											
5011 (6 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	33/2413 (1.4%)	40/2598 (1.5%)	RR 1.18 (0.76 to 1.84)	1 per 100	0 fewer per 100 (0 fewer to 1 more)
Unclear risk of bias (pioglitazone vs. control) (follow-up: range 24-78 weeks)											
3512 (4 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	2/1686 (0.1%)	6/1826 (0.3%)	RR 1.57 (0.53 to 4.69)	0 per 100	0 fewer per 100 (0 fewer to 0 fewer)
High risk of bias (pioglitazone vs. placebo) (follow-up: range 88-192 weeks)											
737 (2 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	18/367 (4.9%)	19/370 (5.1%)	RR 1.05 (0.57 to 1.96)	5 per 100	0 fewer per 100 (2 fewer to 5 more)
High risk of bias (pioglitazone vs. control) (follow-up: range 24-78 weeks)											
2744 (3 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⊕◯◯◯ VERY LOW	14/1708 (0.8%)	4/1036 (0.4%)	RR 0.49 (0.15 to 1.62)	1 per 100	0 fewer per 100 (1 fewer to 1 more)

Abbreviations: **CI:** Confidence interval; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.11.1 GRADE evidence

a. Five studies that carried small weight in high risk of bias studies (pioglitazone vs. placebo (7.1% and 0.2%) and (pioglitazone vs. control (2.8%, 0.4% and 0.3%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (27).

b. The overall imprecision was precise with a significant effect difference (P=0.03). However, all studies reported an overlap CIs, in which (4) studies reported wide CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (412) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.36). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (75) events with large sample size.

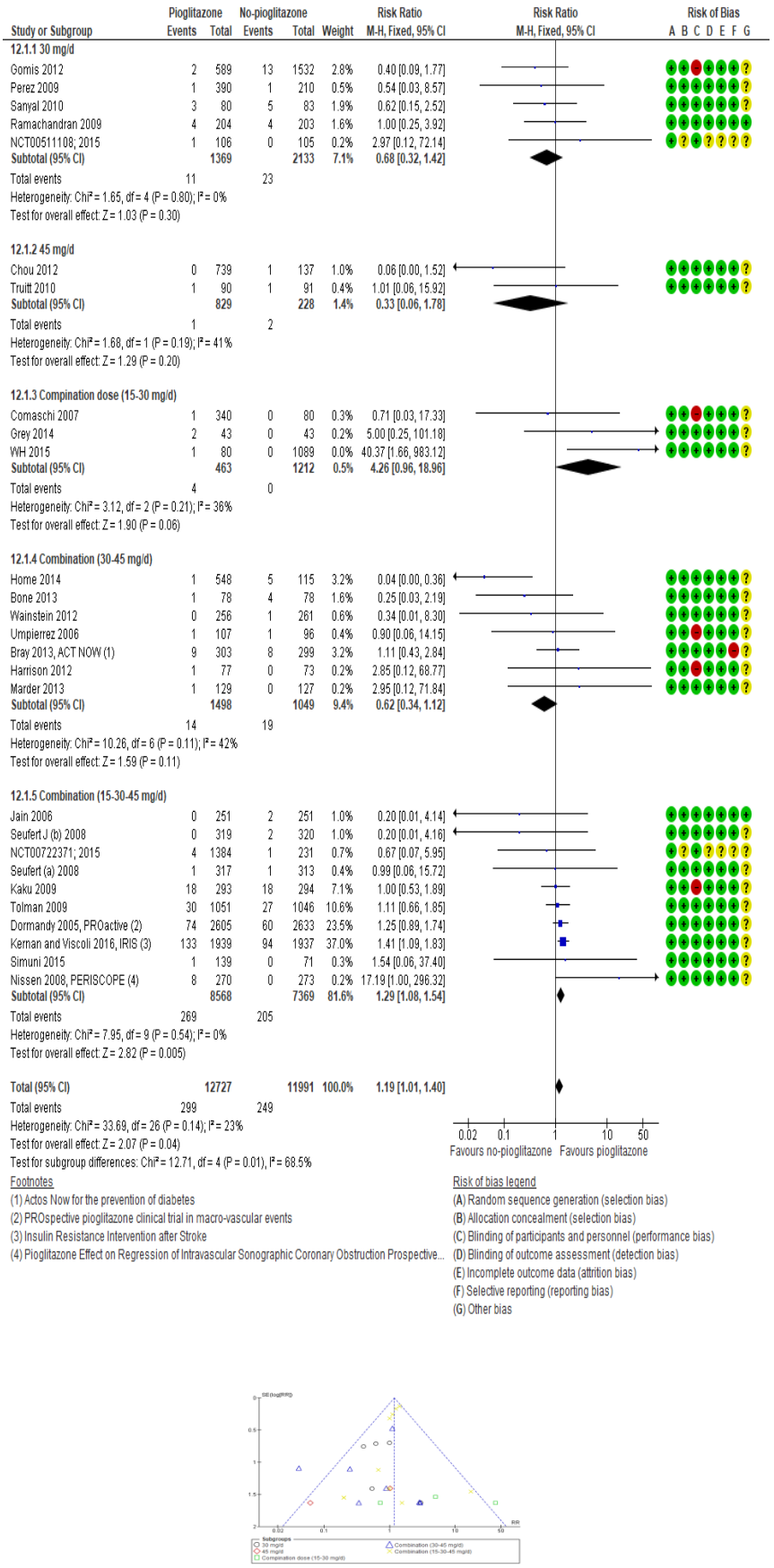
d. The overall imprecision was precise without a significant effect difference (P=0.84). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (6) events with small sample size (1,826).

e. The overall imprecision was precise without a significant effect difference (P=0.87). However, all studies reported overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (37) events with small sample size (737).

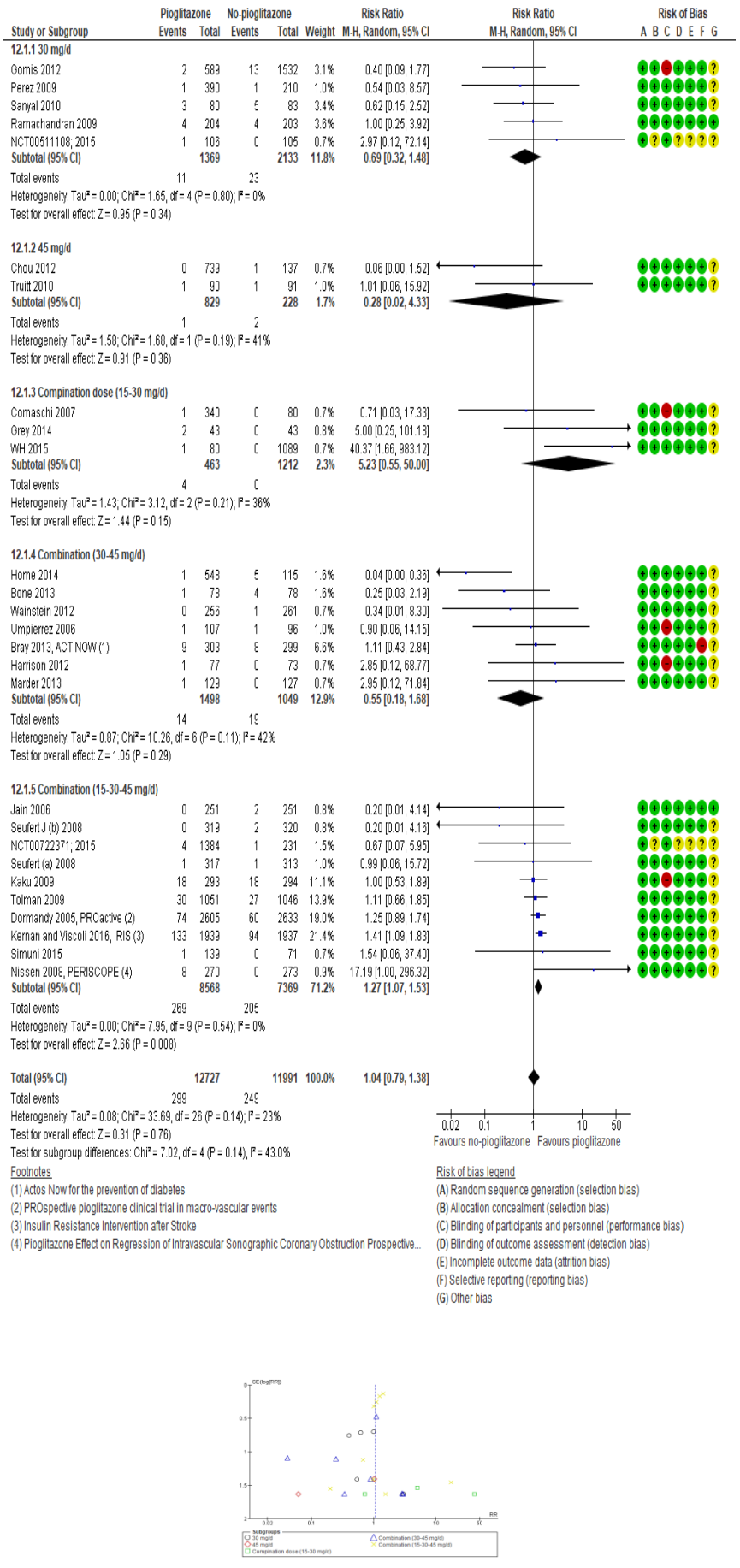
f. The overall imprecision was precise without a significant effect difference (P=0.24). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (18) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a significant effect level of evidence difference (P=0.04). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (37%) and small studies (3.2% and 0.0%) did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (548) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.14; I^2=23%), or a subgroup difference across 5 studies (P=0.67; I^2=0%). Majority of studies at low risk of bias (89.2%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

2.7.12 Pioglitazone fracture by treatment dose



Supplemental Figure 2-16. Forest and funnel plot of pioglitazone fracture by treatment dose, Fixed-effect model.



Supplemental Figure 2-17. Forest and funnel plot of pioglitazone fracture by treatment dose, Random-effect model.

Supplemental Table 2-27. GRADE evidence profile of pioglitazone fracture by treatment dose

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With Pioglitazone		Risk with placebo / controls	Risk difference with pioglitazone
Pioglitazone fracture by treatment dose (follow-up: range 24-251 weeks)											
24718 (27 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	249/11991 (2.1%)	299/12727 (2.3%)	RR 1.19 (1.01 to 1.39)	2 per 100	0 fewer per 100 (0 fewer to 1 more)
30mg/d (follow-up: range 24-157 weeks)											
3502 (5 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ VERY LOW	23/2133 (1.1%)	11/1369 (0.8%)	RR 0.68 (0.32 to 1.42)	1 per 100	0 fewer per 100 (1 fewer to 0 fewer)
45mg/d (follow-up: mean 26 weeks)											
1057 (2 RCTs)	not serious	not serious	not serious	very serious[c]	none	⨁⨁◯◯ LOW	2/228 (0.9%)	1/829 (0.1%)	RR 0.33 (0.06 to 1.78)	1 per 100	1 fewer per 100 (1 fewer to 1 more)
Combination dose (15-30mg/d) (follow-up: range 24-78 weeks)											
1675 (3 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⨁◯◯◯ VERY LOW	0/1212 (0.0%)	4/463 (0.9%)	RR 4.26 (0.96 to 18.96)	0 per 100	0 fewer per 100 (0 fewer to 0 fewer)
Combination (30-45mg/d) (follow-up: range 28-156 weeks)											
2547 (7 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⨁◯◯◯ VERY LOW	19/1049 (1.8%)	14/1498 (0.9%)	RR 0.62 (0.34 to 1.12)	2 per 100	1 fewer per 100 (1 fewer to 0 fewer)
Combination (15-30-45mg/d) (follow-up: range 44-251 weeks)											
15937 (10 RCTs)	serious[a]	not serious	not serious	serious[f]	none	⨁⨁◯◯ LOW	205/7369 (2.8%)	269/8568 (3.1%)	RR 1.29 (1.08 to 1.54)	3 per 100	1 more per 100 (0 fewer to 2 more)

Abbreviations: **CI:** Confidence interval; **mg/d:** milligram pear day; **RCT:** randomise controlled trial; **RR:** Risk ratio.

2.7.12.1 GRADE evidence

a. Five studies that carried small weight ((15, 30, 45mg/d (7.1%), (30mg/d (2.8%), (15-30mg/d (0.3%) and (30-45mg/d (0.4% and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (27).

b. The overall imprecision was precise without a significant effect difference (P=0.30). However, all studies reported overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (34) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.20). However, all studies reported overlap CIs, in which one study reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (3) events with small sample size (1,057).

d. The overall imprecision was precise without a significant effect difference (P=0.06). However, all studies reported overlap and wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (4) events with small sample size (1,675).

e. The overall imprecision was precise without a significant effect difference (P=0.11). However, all studies reported overlap CIs, in which 3 studies reported wide CIs. The 95% CI was not consistent with the possibility for large harm exceeding a minimal important difference, including only (33) events with large sample size.

f. The overall imprecision was precise with a very significant effect difference (P=0.005). However, all studies reported overlap CIs, in which 3 studies reported wide CIs. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including only (474) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a significant effect level of evidence difference (P=0.04). However, the majority of studies reported an overlap CIs, in which (11) reported wide CIs. The largest (37%) and small studies (3.2% and 0.0%) did not cross the line of no difference (1), in which 2 reports a significant association of fracture in the direction of pioglitazone favour across comparators. The 95% CI was consistent with the possibility for large harm exceeding a minimal important difference, including (548) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.14; I^2=23%), but with a subgroup difference across 4 overlap studies (P=0.01; I^2=68.5%). Majority of studies at low risk of bias (89.2%). The overall magnitude of reporting bias was not impact on our results, as these studies conduct as double-blind RCTs, nonetheless. However, our confidence decreased because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 27. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, (2) studies reports an outlier outside the pyramid edge due to multiple interventional groups consequently to very wide CIs.

Chapter 3 New Antidiabetic Drugs and Risk of Stroke: A Systematic Review and Meta-analysis of Randomised Controlled Trials

3.1 Search terms details

A computer assisted literature searches were perform using the Cochrane Library, Ovid Medline, Embase, PubMed and Web of Science databases.

3.1.1 Cochrane Central Register of Controlled Trials (CENTRAL)

#1 [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh stroke]
#2 (isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)):ti,ab,kw
#3 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw
#4 (tia or tias):ti,ab,kw
#5 [mh ^"embolism, paradoxical"]
#6 [mh ^"heart atria"] and ([mh ^embolism] or [mh ^thromboembolism])
#7 ((paradoxic* or crossed) near/5 embolism*):ti,ab,kw
#8 (cryptogenic near/5 stroke):ti,ab,kw
#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10 MeSH descriptor: [Diabetes Mellitus] this term only
#11 ((diabetes or diabetic* or "diabetes mellitus") near/1 ("type 2" or "type II" or "type ii" or "non-insulin dependent" or "non insulin dependent" or "noninsulin dependent" or "adult onset" or "mature onset" or "late onset")).ti,ab,kw
#12 ("diabetes mellitus" not "insulin dependent diabetes mellitus"):kw
#13 NIDDM.ti,ab,kw.
#14 ((diabetic next nephropath*) or “diabetic kidney disease”):ti,ab,kw
#15 (#10 or #11 or # 12 or #13 or #14)
#16 ("dipeptidyl-peptides IV inhibitor" or "dipeptidyl-peptides 4 inhibitor" or "dipeptidyl-peptides IV inhibitors" or "dipeptidyl-peptides 4 inhibitors"):ti,ab,kw
#17 ((DPP4 or DPP 4 or DPP IV) next "inhibitors"):ti,ab,kw
#18 ("alogliptin" or "anagliptin" or "camegliptin" or "dutogliptin" or "gemigliptin" or "linagliptin" or "omarigliptin" or "saxagliptin" or "septagliptin" or "sitagliptin" or "teneligliptin" or "vildagliptin"):ti,ab,kw
#19 gliptin*. ti,ab,kw

#20 incretin*. ti,ab,kw
#21 (#16 or #17 or #18 or #19 or #20)
#22 MeSH descriptor: [Receptors, Glucagon] explode all trees and with qualifier(s): [Agonist - AG]
#23 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees and with qualifier(s): [Agonists & inhibitors - Al]
#24 ("glucagon-like peptide 1 receptor inhibitors" or "glucagon-like peptide 1 receptor agonists" or "glucagon-like peptide 1 inhibitors" or "glucagon-like peptide 1 agonists" or "GLP-1 receptor inhibitors" or "GLP-1 receptor agonists" or "GLP-1 inhibitors" or "GLP-1 agonists"):ti,ab,kw
#25 ("albiglutide" or "dulaglutide" or "exenatide" or "liraglutide" or "lixisenatide" or "semaglutide" or "taspoglutide"):ti,ab,kw
#26 (#22 or #23 or #24 or #25)
#27 MeSH descriptor: [Sodium-Glucose Linked cotransporter 2] explode all trees and with qualifier(s): [Agonists & inhibitors - Al]
#28 ("sodium glucose linked cotransporter 2 inhibitor" or "sodium glucose linked cotransporter ii inhibitor" or "SGLT 2 inhibitor" or "sodium glucose linked cotransporter 2 inhibitors" or "sodium glucose linked cotransporter ii inhibitors" or "SGLT 2 inhibitors"):ti,ab,kw
#29 ("sodium glucose linked cotransporter" near/3 inhibitor*):ti,ab,kw
#30 ("sodium glucose linked co-transporter" near/3 inhibitor*):ti,ab,kw
#31 (canagliflozin or dapagliflozin or empagliflozin or ertugliflozin or ipragliflozin or luseogliflozin or remogliflozin or sergliflozin or tofogliflizin).kw.
#32 gliflozin*.kw.
#35 (#27 or #28 or #29 or #30 or #31 or #32)
#36 randomized controlled trial.pt.
#37 random*.kw.
#38 randomly.ab.
#39 placebo.ab
#40 clinical trial; as topic/
#41 trial.ti,ab,kw
#42 (#36 or #37 or #38 or #39 or #40)
#43 (#9 and #15 and #21 and #42)
#44 limit #43 to humans
#45 (#9 and #15 and #26 and #42)
#46 limit #45 to humans
#47 (#9 and #15 and #35 and #42)
#48 limit #47 to humans
CENTRAL search syntax
The ‘near’ operator defaults to within 6 words;
‘*’ indicates truncation.

3.1.2 MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. tia$1.tw.
5. embolism, paradoxical/
6. heart atria/ and (embolism/ or thromboembolism/)
7. ((paradoxic$ or crossed) adj5 embolism$).tw.
8. (cryptogenic adj5 stroke).tw.
9. or/1-8
10. exp Diabetes Mellitus Type 2/
11. Diabetes Mellitus/
12. ((diabetes or diabetes mellitus or diabetic*) adj1 (type 2 or type II or type ii or non-insulin dependent or noninsulin dependent or adult onset or mature onset or late onset)).tw.
13. NIDDM.tw.
14. Diabetic Nephropathies/
15. (diabetic nephropath* or diabetic kidney disease).tw.
16. or/10-15
17. exp Dipeptidyl Peptides-4 Inhibitors/
18. (dipeptidyl peptide-4* or DPP-4).tw.
19. (alogliptin or anagliptin or camegliptin or dutogliptin or gemigliptin or linagliptin or omarigliptin or saxagliptin or septagliptin or sitagliptin or teneligliptin or vildagliptin).tw.
20. gliptin*.tw.
21. incretin*.tw.
22. (dpp adj (4 or IV)).tw.
23. or/17-22
24. exp Glucagon-Like Peptides/
25. (glucagon-like peptide 1 receptor inhibitor* or glucagon-like peptide 1 receptor agonist* or glucagon-like peptide 1 inhibitor* or glucagon-like peptide 1 agonist* or GLP-1 receptor inhibitor* or GLP-1 receptor agonist* or GLP-1 inhibitor* or GLP-1 agonist*).tw.
26. (albiglutide or dulaglutide or exenatide or liraglutide or lixisenatide or semaglutide or taspoglutide).tw.
27. glutide*.tw.
28. or/24-27
29. exp sodium-glucose linked cotransporter-2/
30. (sodium-glucose linked cotransporter 2 inhibitor* or sodium-glucose linked cotransporter ii inhibitor* or SGLT-2 inhibitor*).tw.
31. (sodium-glucose linked cotransporter adj3 inhibitor*).tw.
32. (sodium-glucose linked co transporter adj3 inhibitor*).tw.

33. (canagliflozin or dapagliflozin or empagliflozin or ertugliflozin or ipragliflozin or luseogliflozin or remogliflozin or sergliflozin or tofogliflizin).tw.
34. gliflozin*.tw.
35. or/29-34
36. Randomised Controlled Trials as Topic/
37. random allocation/
38. Controlled Clinical Trials as Topic/
39. control groups/
40. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
41. double-blind method/
42. single-blind method/
43. Placebo/
44. placebo effect/
45. Drug Evaluation/
46. Research Design/
47. randomised controlled trial.pt.
48. controlled clinical trial.pt.
49. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
50. random$.tw.
51. (controlled adj5 (trial$ or stud$)).tw.
52. (clinical$ adj5 trial$).tw.
53. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
54. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
56. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
57. placebo$.tw.
58. controls.tw.
59. (RCT or RCTs).tw. or trial.ti.
60. or/36-59
61. 9 and 16 and 23 and 42
62. limit 61 to humans
63. 9 and 16 and 28 and 42
64. limit 63 to humans
65. 9 and 16 and 35 and 42
66. limit 65 to humans

Ovid search syntax

.pt. denotes a Publication Type term;

.ab. denotes a word in the abstract;

.sh. denotes a Medical Subject Heading (MeSH) term;

.ti. denotes a word in the title;

The ‘adj6’ operator indicates within 6 words;

.mp. indicates a search of title, original title, abstract, name of substance word and subject heading word;

‘$’ the dollar sign ($) stands for any character(s) indicates truncation;
tw. text word.

3.1.3 EMBASE search strategy

1. cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. tia$1.tw.
5. paradoxical embolism/
6. exp heart atrium/ and (embolism/ or thromboembolism/)
7. ((paradoxic$ or crossed) adj5 embolism$).tw.
8. (cryptogenic adj5 stroke).tw.
9. or/1-8
10. diabetes mellitus/
11. non insulin dependent diabetes mellitus/
12. ((diabetes or diabetes mellitus or diabetic*) adj1 (type 2 or type II or type ii or non-insulin dependent or noninsulin dependent or adult or adult onset or mature onset or late onset)).tw.
13. NIDDM.tw.
14. diabetic nephropathy/
15. (diabetic nephropath* or diabetic kidney disease).tw.
16. or/10-15
17. dipeptidyl peptidase IV inhibitor/
18. (dipeptidyl-peptidase IV inhibitor* or dipeptidyl-peptidase 4 inhibitor* or ((DPP4 or DPP 4 or DPP IV) adj inhibitor*)).tw.
19. (alogliptin or anagliptin or camegliptin or dutogliptin or gemigliptin or linagliptin or omarigliptin or saxagliptin or sitagliptin or teneligliptin or vildagliptin).tw.
20. or/17-19
21. glucagon like peptide 1 receptor agonist/
22. (glucagon-like peptide 1 receptor inhibitor* or glucagon-like peptide 1 receptor agonist* or glucagon-like peptide 1 inhibitor* or glucagon-like peptide 1 agonist* or GLP-1 receptor inhibitor* or GLP-1 receptor agonist* or GLP-1 inhibitor* or GLP-1 agonist*).tw.
23. (albiglutide or dulaglutide or exenatide or liraglutide or lixisenatide or semaglutide or taspoglutide).tw.
24. 21 or 23
25. sodium glucose linked cotransporter 2 inhibitor/
26. (sodium glucose linked cotransporter 2 inhibitor* or sodium glucose linked cotransporter ii inhibitor* or SGLT 2 inhibitor*).tw.
27. (sodium glucose linked cotransporter adj3 inhibitor*).tw.
28. (sodium glucose linked co transporter adj3 inhibitor*).tw.

29. (canagliflozin or dapagliflozin or empagliflozin or ertugliflozin or ipragliflozin or luseogliflozin or remogliflozin or sergliflozin or tofogliflizin).tw.
30. gliflozin*.tw.
31. or/25-30
32. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
33. Randomization/
34. Controlled clinical trial/ or "controlled clinical trial (topic)"/
35. control group/ or controlled study/
36. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
37. Double Blind Method/
38. Single Blind method/ or triple blind method/
39. (random$ or RCT or RCTs).tw.
40. (controlled adj5 (trial$ or stud$)).tw.
41. (clinical$ adj5 trial$).tw.
42. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
43. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
44. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
45. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
46. trial.ti
47. assign$.tw.
48. random allocation/
49. allocat$.tw.
50. controls.tw.
51. placebo$.tw.
52. placebo effect/
53. Drug Evaluation/
54. Research Design/
55. or/31-54
56. 9 and 16 and 20 and 55
57. limit 56 to humans
58. 9 and 16 and 24 and 55
59. limit 58 to humans
60. 9 and 16 and 31 and 55
61. limit 60 to humans

Unless otherwise stated, search terms are free text terms; MeSH or [mh] = Medical subject heading (MEDLINE medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) substitutes one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent (i.e. number of words within range of search term).

3.1.4 Web of Science search strategy

1. Stroke AND diabetes mellitus type 2 AND dipeptidyl peptidase-4 inhibitors.

2. Stroke AND diabetes mellitus type 2 AND glucagon-like peptide-1 agonist.
3. Stroke AND diabetes mellitus type 2 AND sodium-glucose cotransporter-2 inhibitors.

Articles identified through Cochrane Library **18**, MEDLINE **62**, EMBASE **662**, Web of Science **229** and **94** publications through Grey Literature.

3.2 Ongoing and excluded studies

Supplemental Table 3-1. Ongoing studies

Study Expected date of publication	Primary outcome	Population	Mean age‡ Males (%) Intervention/control	Study design and country	Parallel arms	Intervention groups	Background therapy	Intervention dosage‡	Duration (weeks)
EUCTR 2013-001558-87	Safety of exenatide in acute ischemic stroke patients treated with intravenous thrombolysis	T2DM with acute ischaemic stroke on intravenous thrombolysis (*n*= 40)	NR	Open-label, RCT, in 5 centres in Sweden	2	Exenatide vs. placebo	NR	5 µg/day	NR
EUCTR 2011-002780-16	MACEs outcomes	T2DM with acute stroke (*n*= 100)	NR	Open-label, RCT, in Sweden, PROLOGUES trial	2	Exenatide vs. intermittent insulin	NR	10 µg/day	NR
EUCTR 2011-003572-36	MACEs outcomes	T2DM with impaired swallowing with acute stroke (*n*= 40)	NR	Open-label, RCT, LAST trial in UK	2	Liraglutide vs. standard care	NR	NR	24
NCT01986881 2020	MACEs outcomes	T2DM wit established CVD (*n*=8000)	NR	Phase III, double-blind, RCT, in 149 centres in 23 countries, VERTIS CV trial	3	Ertugliflozin vs. placebo	NR	5-15 mg/day	60-84
NCT02397421 2020	MACEs outcomes	T2DM left ventricular remodelling in patients with HF (*n*=NR)	NR	Phase IV, double-blind, RCT, REFORM trial	2	Dapagliflozin vs. placebo	NR	10 mg/day	48

Abbreviations: *CVD*, cardiovascular disease; *mg/d*, milligram pear day; *NR*, not report; *MACEs*, major adverse cardiovascular events; *MI*, myocardial infarction; *RCT*, randomised controlled trial; *T2DM*, type 2 diabetes mellitus.
Note: ‡ Mean age and dosages present for intervention drugs.

Supplemental Table 3-2. Excluded studies

Study	Reasons	Population	Mean age‡ Males (%) Intervention/control	Study design and country	Parallel arms	Intervention groups	Background therapy	Intervention dosage‡	Duration (weeks)
NCT01778049	All participants randomised to empagliflozin	T2DM (*n*=1184)	56.8/NR 56.6/NR	Phase III, double-blind, parallel-group, RCT, in 114 centres in 11 countries	8	Linagliptin/empagliflozin¶ vs. placebo	Metformin	Linagliptin 5 mg/day Empagliflozin 10-25 mg/day	24
Gomis 2012 NCT00736099	All randomised arms receive linagliptine	T2DM (*n*=2122)	57.8/56.7 51.5/52.6	Phase III, open-label, parallel-group, RCT, in 232 centres in 32 countries	2	Linagliptine vs. linagliptine + pioglitazone	NR	5 mg/d	78
Kashiwagi 2011 NCT00372060	All randomised arms receive sitagliptin	T2DM (*n*=134)	57.8/59 57.6/72.1	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. sitagliptin + placebo	Pioglitazone	50-100 mg/d	52
NCT00306384	All randomised arms receive sitagliptin; as an open-label extension period of 7 phase III trials; (NCT00286455, NCT00286468, NCT00286442, NCT00286494, NCT00286429, NCT00328627, NCT00395512)	T2DM (*n*=3320)	55.8/55.1 49.9/47.8	Phase III, open-label, parallel-group, RCT, in 155 centres in 12 countries	2	Sitagliptin	NR	12.5-25 mg/d	209
NCT01255163	Alzheimer's disease not T2DM	NR	NR	Phase II, double -blind, RCT, in USA	1	Exenatide vs. placebo	NR	NR	78
NCT01843075	Alzheimer's disease not T2DM	NR	NR	Phase II, double -blind, RCT, in 659 sites in 34 countries, ELAD trial	2	Iraglutide vs. placebo	NR	1.8 mg/day	52
NCT01051011	High discontinuation rates mainly due to GI tolerability and implementation of risk mitigation plan to address hypersensitivity reactions	T2DM (*n*=500-600)	NR	Phase III, open-label, RCT multicentre	3	Taspoglutide vs. placebo	Metformin ± sulfonylurea	10-20 mg/day	52
Neal 2017 NCT01032629 NCT01989754	Stroke outcomes report as number of participants per 1000 patient year	T2DM with high CVD (*n*=10142)	64.9/63.3	Phase III, double-blind, RCT, in 667 centres in 30 countries, CANVAS and CANVAS-R trial	2	Canagliflozin vs. placebo	NR	100-300 mg/d	188.2
NCT02065791 11/2019	Renal and vascular outcomes No stroke outcomes	T2DM with stage II/III CKD on ACE/ARB (*n*=3700)	NR	Phase III, double-blind, RCT, in 590 centres in 34 countries, CREDENCE trial	2	Canagliflozin vs. placebo	NR	100 mg/d	287

Abbreviations: *ACE*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptors blocker; *CAD*, coronary artery disease; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *mg/d*, milligram pear day; *NR*, not report; *MACEs*, major adverse cardiovascular events; *RCT*, randomised controlled trial; *T2DM*, type 2 diabetes mellitus.
Note: ‡ Mean age and dosages present for intervention drugs.

3.3 Categorisation of the anti-hyperglycaemic therapies

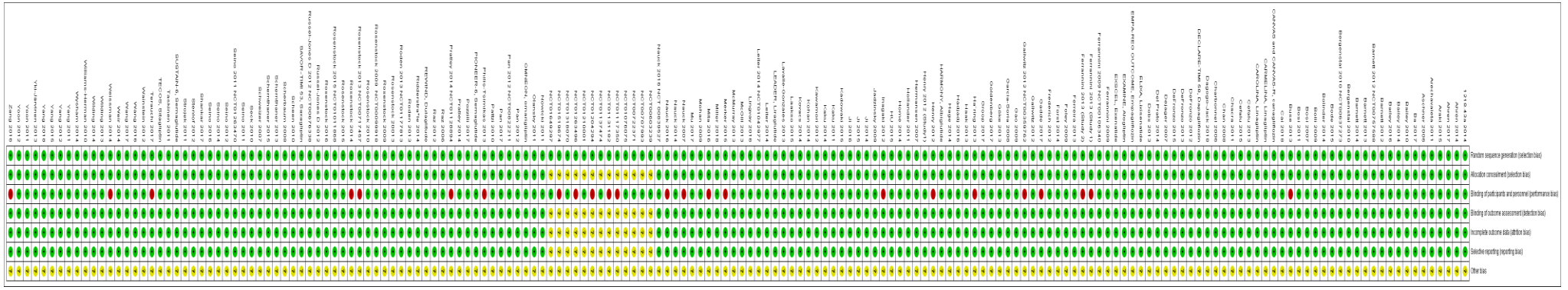
Supplemental Table 3-3. Categorisation of the anti-hyperglycaemic therapy

Anti-hyper glycaemic agents (Generic Name)	Anti-hyper glycaemic agents (Trade Name)	Mechanism of action
TZDs class:		
Pioglitazone	Actos	TZDs: activating PPARs.
Rosiglitazone	Avandia	Stimulates the nuclear receptor PPAR-γ and to a lesser extent PPAR-α. It modulates genes transcription involved in control of glucose and lipid metabolism in muscle, adipose tissue, liver.
Rivoglitazone	-	
Pioglitazone/metformin	Actoplus Met, Piomet or	
Pioglitazone/alogliptin¶	Incresync or Oseni	Selective ligand of PPARγ and has no PPARα-binding action.
Pioglitazone/linagliptin¶	Janacti	Dual peroxisome proliferator-activated receptor α/γ agonist
Pioglitazone/sitagliptin¶	Politor	
Rosiglitazone/metformin¶	Avandment	
Aleglitazar	-	
Biguanide class:		
Metformin	Glucophage	Metformin: improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Metformin/glibenclamide¶	-	
Metformin/gliclazide¶	-	
Metformin/saxagliptin¶	Kombiglyze XR	
Metformin/sitagliptin¶	Janumet	
Sulfonylurea class:		Sulfonylureas bind to an ATP-sensitive K^+ (KATP) channel on the cell membrane of pancreatic β cells. This inhibits a tonic, hyperpolarizing efflux of K^+, causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular Ca^{2+} leads to increased fusion of insulin granulae with the cell membrane and therefore increased secretion of (pro) insulin.
Glibenclamide	Glyburide	
Gliclazide	Diamicron	
Glimepiride	Amaryl	
Glipizide	Glucotrol	
Glinides	Meglitinides	
DPP4-Is class:		
Alogliptin	Nesina or Vipidia	Glucagon increases blood glucose levels and DPP4-Is reduce glucagon and blood glucose levels. The mechanism of DPP4-Is is to increase incretin levels (GLP1-RAs), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying and decreases blood glucose levels.
Dutogliptin	BI-1356 or Tradjenta	
Linagliptin	MK-3102	
Omarigliptin	BMS-477118 or Onglyza	
Saxagliptin	MK-0431 or Januvia	
Sitagliptin	Tenelia	
Teneligliptin	Galvus or Zomelis	
Vildagliptin		
GLP1-RAs class:		GLP1-RAs is a potent antihyperglycemic hormone, inducing the β-cells of the pancreas to release the hormone insulin in response to rising glucose, while suppressing glucagon secretion.
Long-acting GLP1-RAs:	Eperzan and Tanzeum	
Albiglutide	LY2189265	
Dulaglutide	Byetta or Bydureon	
Exenatide	NN2211 or Victoza	
Liraglutide	Rybelsus or Ozempic	
Semaglutide	Lyxumia	
Short-acting GLP1-RAs:	Eperzan	
Lixisenatide		
Taspoglutide		
SGLT2-Is class:		SGLT2-Is is called gliflozins and lead to a reduction in blood glucose levels. Therefore, SGLT2 inhibitors have potential use in the treatment of T2DM. As studied on canagliflozin, a member of this class of drugs, gliflozins enhance glycemic control as well as reduce body weight and systolic and diastolic blood pressure.
Canagliflozin	Invokana or Sulisent	
Dapagliflozin	Farxiga or Forxiga	
Empagliflozin	Jardiance	
Ertugliflozin	Steglatro	
Insulin class:		
Insulin aspart	NovoLog/NovoRapid	Fast and short-acting
Insulin degludec	Tresiba	Ultralong-acting insulin
Insulin glargine	Lantus	Long-acting basal insulin
Insulin lispro	Humalog	Fast and short-acting

Abbreviations: *DPP4-Is*, dipeptidyl peptidase-4 inhibitor; *GLP1-RAs*, glucagon-like peptide-1 receptor agonist; *SGLT-2*, sodium glucose co-transporter-2 inhibitor; *PPARs*, peroxisome proliferator-activated receptors.
Note: ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG.

3.4 Risk of bias outcomes

Supplemental Figure 3-1. Risk of bias outcomes in individuals' studies included in the meta-analysis



3.5 Studies characteristics outcome

3.5.1 DPP4-Is therapies

Supplemental Table 3-4. Baseline characteristics of DPP4-Is therapies included trials

Study Trial registry	Population Sample size	T2DM† mean duration (years)	HbA1c levels %	Prior stroke / TIA (*n.*, %)	Mean age (years)‡	Males (%)	Study design and country	Parallel arms	DPP4-Is vs. comparators	Background AHGs therapy	DPP4-Is dosage‡ mg/day	Duration (weeks)
Alogliptin therapy												
DeFronzo 2008 [530] NCT00286455	T2DM (*n*=328)	6.9±5.9/6.9±5.9	7.9±0.1/7.9±0.1	NR	53.4/53.4	53.9/50.7	Phase III, double-blind, parallel-group, RCT, in 67 centres in 18 countries	3	Alogliptin vs. placebo	None	12.5-25	26
Nauck 2009 [531] NCT00286442	T2DM (*n*=527)	6.0±5.0/6.0±5.0	7.9±0.7/8.0±0.9	NR	54.5/56.0	50.8/50.0	Double-blind, parallel-group, RCT, in 115 centres in 15 countries	3	Alogliptin vs. placebo	Metformin	12.5-25	26
Pan 2017 [532] NCT01289119	T2DM (*n*=505)	4.3±2.8/2.1±2.8	8.0/8.0	NR	78.6/52.7	52.4/56.3	Phase III, double-blind, parallel-group, RCT, in 30 centres in 3 countries	6	Alogliptin vs. placebo	None ± pioglitazone ± metformin	25	16
Pratley 2009 [533] NCT00286494	T2DM (*n*=434)	7.5±5.5/7.8±6.7	8.1±0.9/8.0±0.8	NR	55.4/55.2	59.1/54.6	Phase III, double-blind, parallel-group, RCT, 125 centres in 8 countries	3	Alogliptin vs. placebo	Metformin ± Pioglitazone ± sulfonylurea	12.5-25	24
White 2013 [386] NCT00968708	T2DM with ACS (*n*=5380)	7.3±2.8/8.0±1.1**	7.1±2.6/8.0±1.1**	Stroke 193 (7.2%) vs. 195 (7.2%)	61.0/61.0**	67.7/68.0	Double-blind, parallel-group, RCT, in 918 centres in 50 countries, EXAMINE trial	2	Alogliptin[a] vs. placebo	Metformin + sulfonylurea + TZDs +insulin	6.25, 12.5, 25	78
Rosenstock 2009 [534] NCT00286429	T2DM (*n*=389)	12.7±6.7/9.3±1.1	12.2±7.1/9.3±1.1	NR	56.0/55.0	41.3/47.7	Phase III, double-blind, parallel-group, RCT, in 60 centres in 16 countries	3	Alogliptin vs. placebo	Insulin ± metformin	12.5, 25	26
Seino 2012 [535] NCT01318083; NCT01318135	T2DM (*n*=312)	9.9±6.9/8.5±0.8	9.4±7.4/8.6±0.8	NR	60.1/60.3	68.5/71.0	Phase II/III, double-blind, parallel-group, RCT, in Japan	3	Alogliptin vs. placebo	Sulfonylurea (glimepiride)	12.5, 25	24
Pratley 2009 [536] NCT00286468	T2DM (*n*=500)	7.7±6.1/7.7±5.3	8.0/8.0	NR	56.5/57.1	52.4/51.5	Phase III, double-blind, parallel-group, RCT, in 124 centres in 16 countries	3	Alogliptin vs. placebo	Sulfonylurea	12.5-25	26
Seino 2011 [537] NCT01263483	T2DM (*n*=230)	7.9±5.5/7.5±6.0	7.9±0.9/8.1±1.2	NR	61.5/62.3	60.6/64.0	Phase II/III, double-blind, parallel-group, RCT	3	Alogliptin vs. placebo	α-glucosidase Is + voglibose	12.5-25	12
DeFronzo 2012 [496] NCT00328627	T2DM (*n*=1553)	5.9±5.3/6.0±5.0	8.6±0.7/8.5±0.6	NR	54.0/54.9	41.0/46.0	Phase III, double-blind, parallel-group, RCT, in 90 centres in 19 countries	12	Alogliptin vs. placebo + pioglitazone	Metformin	12.5-25	26
Seino 2011 [538] NCT01263470	T2DM (*n*=480)	6.6±6.2/6.4±6.0	7.9±0.9/7.9±0.9	NR	58.7/59.1	58.2/56.0	Phase II, double-blind, parallel-group, RCT, in 54 centres in Japan	6	Alogliptin vs. placebo + α-glucosidase-Is (voglibose)	None	Alogliptin 6.25, 12.5, 25, 50	52
NCT01263496 [539]	T2DM (*n*=474)	NR	NR	NR	64.0/64.0	82/67.5	Phase III, open-label, parallel-group, RCT, in Japan	5	Alogliptin vs. α-glucosidase-Is (voglibose)	None	Alogliptin 6.25, 12.5, 25, 50	52
Pratley 2014 [540] NCT01023581	T2DM (*n*=768)	3.9/4.0	8.5/8.5	NR	53.6/53.3	55.2/50.5	Phase III, double-blind, parallel-group, RCT, in 201 centres in 13 countries, AM7D trial	7	Alogliptin vs. placebo + metformin	None	Alogliptin 12.5, 25 Alogliptin + metformin¶ 12.5/500, 12.5/1000	34
Bosi 2011 [506] NCT00432276	T2DM (*n*=803)	7.2±5.2/6.9±4.6	8.3±0.8/8.1±0.8	NR	54.3/55.9	51.9/51.1	Phase III, double-blind, parallel-group, RCT, in 86 centres in USA	2	Alogliptin vs. metformin + pioglitazone	Metformin + pioglitazon	25	52
NCT00707993 [541]	T2DM (*n*=441)	6.3±6.3/5.9±6.3	NR	NR	70.1/69.8	45.9/43.8	Double-blind, parallel-group, RCT, in 80 centres in 11 countries	2	Alogliptin vs. glipizide	None	25	52
Del Prato 2014 [542] NCT00856284	T2DM (*n*=2620)	5.5±5.0/5.5±4.9	7.6±0.6/7.6±0.6	NR	55.4/55.4	49.4/50.5	Phase III, double-blind, parallel-group, RCT, ENDURE trial in 262 centres in 31 countries	3	Alogliptin vs. glipizide	Metformin	12.5-25	104
Rosenstock 2010 [497] NCT00395512	T2DM (*n*=654)	3.2±3.5/3.2±3.7	8.8±1.0/8.8±1.0	NR	53.0/51.5	46.7/55.2	Phase III, double-blind, parallel-group, RCT, in 161 centres in 23 countries	4	Alogliptin vs. pioglitazone	Pioglitazone	12.5-25	26
NCT01318070 [543]	T2DM (*n*=339)	NR	NR	NR	≥/≤65	61.2/66.1	Phase II/III, double-blind, parallel-group, RCT, in 52 centres in Japan	3	Alogliptin vs. pioglitazone	Pioglitazone	12.5-25	12

Mita 2016 [544] UMIN000005311	T2DM with CVD (carotid atherosclerosis) (*n*=322)	9.0(5.0-15.0)/8.2(4.0-15.0)**	7.3±0.8/7.2±0.8	NR	64.4/64.8	63.0/61.0	Open-label, blind-end point (PROBE), in 11 centres in Japan, SPEAD-A	2	Alogliptin vs. conventional treatment (other than DPP-4 Is)	Metformin + sulfonylurea + glinides + TZDs + α-glucosidase-Is	25	104
Dutogliptin therapy												
Pattzi 2010 [545]	T2DM (*n*=422)	NR	8.5±1.0/8.4±1.1	NR	53.0/53.0	53.5/52.3	Phase III, double-blind, parallel-group, RCT, in 73 centres in 5 countries	3	Dutogliptin vs. placebo	Metformin ± TZDs	200, 400	12
Garcia-Soria 2008 [546]	T2DM (*n*=174)	5.5±3.5/5.2±2.7	8.7±1.0/8.7±1.0	NR	52.6/51.0	42.0/39.0	Double-blind, parallel-group, RCT, in 26 centres in USA, Mexico and Australia	4	Dutogliptin vs. placebo	Metformin ± glitazone	100, 200, 400	4
Linagliptin therapy												
Rosenstock 2019 [387] NCT01897532	T2DM with CVD and/or CKD (*n*=6979)	14.8±9.6/14.3±9.2	7.9±1.0/7.9±1.0	NR	66.2/65.7	60.7/63.9	Phase IV, double-blind, parallel-group, RCT, in 605 centres in 27 countries, CARMELINA trial	2	Linagliptin vs. placebo	Metformin ± sulfonylurea ± insulin	5	224**
Del Prato 2010 [547] NCT00621140	T2DM (*n*=503)	NR	8.0±0.9/8.0±0.9	NR	56.4/54.4	48.8/47.3	Phase III, double-blind, parallel-group, RCT, in 69 centres in 11 countries	2	Linagliptin vs. placebo	None	5	24
Taskinen 2011 [548] NCT00601250	T2DM (*n*=700)	≤1->5/≤1->5	8.1±0.9/8.0±0.9	NR	56.5/56.6	53.2/57.1	Phase III, double-blind, parallel-group, RCT, in 82 centres in 10 countries	2	Linagliptin vs. placebo	Metformin	5	24
Haak 2012 [549] NCT00798161	T2DM (*n*=757)	≤1->5/≤1->5	8.7±1.0/8.6±1.0	NR	50.4/45.1	50.4/45.1	Phase III, double-blind, parallel-group, RCT, in 138 centres in 14 countries	7	Linagliptin vs. placebo	Metformin	2.5, 5	24
Søfteland 2017 [550] NCT01734785	T2DM (*n*=716)	≤1->10/≤1->10	7.9±0.8/7.9±0.8	NR	54.9/55.9	61.7/55.5	Phase III, double-blind, parallel-group, RCT, in 90 centres in 11 countries	2	Linagliptin vs. placebo	Metformin	5	24
Owens 2011 [551] NCT00602472	T2DM (*n*=1055)	≤1->5/≤1->5	8.2±0.0/8.1±0.1	NR	58.3/57.6	46.8/48.3	Phase III, 24 week double-blind, 52 week open-label, parallel-group, RCT, in 100 centres in 11 countries	2	Linagliptin vs. placebo	Metformin + sulfonylurea	5	76
Bajaj 2014 [552] NCT00996658	T2DM (*n*=272)	≤1->5/≤1->5	8.4±0.8/8.5±0.7	NR	53.1/55.2	45.4/55.1	Phase III, double-blind, parallel-group, RCT, in 52 centres in 3 countries	2	Linagliptin vs. placebo	Metformin + pioglitazone	5	24
Barnett 2013 [553] NCT01084005	T2DM (*n*=241)	≤1->5/≤1->5	7·8±0·8/7·7±0·7	NR	74.9/74.9	71.6/62.0	Phase III, double-blind, parallel-group, RCT, in 34 centres in 5 countries	2	Linagliptin vs. placebo	Metformin ± sulfonylurea ± basal insulin	5	24
Lewin 2012 [554] NCT00819091	T2DM (*n*=245)	≤1->5/≤1->5	8.60.9/8.60.7	NR	57.2/56.2	47.8/61.9	Phase III, double-blind, parallel-group, RCT, in 45 centres in 7 countries	2	Linagliptin vs. placebo	Sulfonylurea	5	18
Gomis 2011 [555] NCT00641043	T2DM (*n*=389)	NR	8.6±0.9/8.6±0.8	NR	57.7/57.1	58.7/65.4	Phase III, double-blind, parallel-group, RCT, in 43 centres in 7 countries	2	Linagliptin vs. placebo	Pioglitazone	5	24
Yki-Järvinen 2013 [556] Duran-Garcia 2015 NCT00954447	T2DM (*n*=1261)	≤1->5/≤1->5	8.3±0.8/8.3±0.9	NR	59.7/60.4	52.1/52.2	Phase III, double-blind, parallel-group, RCT, in 169 centres in 19 countries	2	Linagliptin vs. placebo	Basal insulin + metformin ± pioglitazone	5	52
Wang 2016 [557] NCT01215097	T2DM (*n*=305)	NR	7.9±0.8/8.0±0.8	NR	55.1/56.5	49.8/50.0	Phase III, double-blind, parallel-group, RCT, in 19 centres in 3 countries	2	Linagliptin vs. placebo	Metformin ± sulfonylurea ± α-glucosidase-Is ± other AHGs	5	24
1218.43[a] 2014 [558] NCT00800683	T2DM with CKD[d] (*n*=133)	NR	8.2±1.1/8.2±0.9	NR	64.0/64.9	66.2/53.8	Phase III, double-blind, parallel-group, RCT, in 53 centres in 6 countries	2	Linagliptin vs. placebo	Pioglitazone, sulfonylurea, glinides, α-glucosidase-Is + insulin	5	52
McGIll 2013 [559] PMCID: PMC3554278	T2DM with CKD[d] (*n*=133)	≤1->5/≤1->5	8.2±1.1/8.2±0.9	NR	64.0/54.9	66.2/53.8	Phase III, double-blind, parallel-group, RCT, in 53 centres in 6 countries	2	Linagliptin vs. placebo	Sulfonylurea, glinides, pioglitazone, α-glucosidase-Is, insulin	5	55
Groop 2017 [560] NCT01792518	T2DM with CKD on ACE ± ARB (*n*=360)	≤1->10/≤1->10	7.8±0.9/7.9±0.9	NR	61.0/60.1	63.7/63.5	Phase IIIb, double-blind, parallel-group, RCT, in 74 centres in 12 countries, MARLINA-T2D trial	2	Linagliptin vs. placebo	NR	5	24
Kawamori 2012 [561] NCT00654381	T2DM (*n*=561)	≤1->5/≤1->5	8.0±0.7/7.9±0.5/8.0±0.7	CVA 168 (52.7%) vs. 90 (55.6%) vs. 36 (45.0%) vs.	60.8/59.7/58.5	69.9/71.3/70.9	Phase IIb/III, double-blind, parallel-group, RCT, in 47 centres in Japan	4	Linagliptin vs. placebo + α-glucosidase-Is (voglibose)	None	5, 10	26

Mu 2017 [562] NCT01708902	T2DM (*n*=1002)	≤1-≤10/≤1-≤10	10.3±0.9/8.7±1.0	NR	51.0/51.8	69.0/63.0	Phase III, double-blind, parallel-group, RCT, in 56 centres in 4 countries	6	Linagliptin/metformin[$] vs. metformin	None	2.5-5	24
Haak 2013 [563] NCT00915772	T2DM (*n*=566)	≤1->5/≤1->5	7.5±1.1/7.5±0.9	NR	55.9/55.6	54.8/54.7	Phase III, double-blind, parallel-group, RCT, in 112 centres in 14 countries	3	Linagliptin vs. metformin	Metformin	2.5/500 2.5/1000	54
NCT01204294; 2104 [499]	T2DM (*n*=574)	NR	NR	NR	60.8/61.2	69.7/69.8	Phase III, open-label, parallel-group, RCT, in 43 centres in Japan	7	Linagliptin vs. metformin	AHG agents	5	52
Barnett 2012 [564] NCT00740051	T2DM (*n*=227)	≤1->5/≤1->5	8.1±1.0/8.1±0.9	NR	56.4/56.7	36.4/43.4	Phase III, double-blind, parallel-group, RCT, 53 centres in 7 countries	2	Linagliptin vs. placebo + sulfonylurea	None	5	52
Laakso 2015 [565] NCT01087502	T2DM with CKD (*n*=235)	NR	8.4±0.9/8.0±0.9	NR	67.3/65.9	61.9/64.8	Phase III, double-blind, parallel-group, RCT, in 52 centres in 9 countries	2	Linagliptin vs. placebo + glimepiride	None or TZDs + α-glucosidase-Is ± insulin	5	52
Gallwitz 2012 [399] NCT00622284	T2DM (*n*=1551)	≤1->5/≤1->5	7·7±0·9/7·7±0·9	NR	59.8/59.8	60.0/61.0	Double-blind, parallel-group, RCT, in 209 centres in 16 countries	2	Linagliptin vs. glimepiride	Metformin	5	104
Rosenstock 2019 [388] NCT01243424	T2DM with high risk CVD (*n*=6072)	6.3 (3.0,11.1)/6.2 (2.9,10.9)[**]	7.2/7.2	CVD 371 (12.3%) vs. 356 (11.9%)	603.9/64.2	60.8/59.2	Phase III, double-blind, RCT, in 612 centres in 43 countries, CAROLINA trial	4	Linagliptin vs. glimepiride	NR	5	432
Omarigliptin therapy												
Gantz 2017 [389] NCT01703208	T2DM with established CVD (*n*= 4202)	12.0±7.6/12.1±8.0	8.0±0.9/8.0±0.9	NR	63.7/63.6	69.6/70.0	Phase III, double -blind, RCT, multicentre, OMNEON trial	2	Omarigliptin vs. placebo	Metformin ± pioglitazone ± SGLT-2I ± α-glucosidase inhibitor	25	156
Goldenberg 2017 [566] NCT01841697	T2DM (*n*=642)	7.0±4.5/7.5±5.6	7.5±0.7/7.5±0.8	NR	57.0/57.6	46.9/54.7	Phase III, double-blind, parallel-group, RCT	2	Omarigliptin vs. sitagliptin	Metformin	Omarigliptin 25 Sitagliptin 100	24
Saxagliptin therapy												
Pan 2012 [567] NCT00698932	T2DM (*n*=496)	0.8±1.4/8.1±0.8	1.2±2.6/8.2±0.8	NR	51.2/51.6	56.3/54.6	Phase III, double-blind, parallel-group, RCT, in Asian patients	2	Saxagliptin vs. placebo	None	5	24
Rosenstock 2008 [568] NCT00950599	T2DM (*n*=423)	1.0±15.5/1.8±23.0 [**]	7.9±1.2/8.0±0.9	NR	53.3/54.0	57.7/59.4	Phase II, double-blind, parallel-group, RCT, 152 centres in USA	8	Saxagliptin vs. placebo	None	2.5, 5, 10, 20, 40, 100	18
Kumar 2014 [569] NCT00918879	T2DM (*n*=213)	0.8±1.2/1.0±1.4	8.3±0.8/8.3±0.7	NR	49.1/48.3	53.3/59.4	Phase III-b, double-blind, parallel-group, RCT, in India	2	Saxagliptin vs placebo	None	5	24
Frederich 2012 [570] NCT00316082	T2DM (*n*=365)	1.7±3.0/1.7±2.8	7.9±0.9/7.8±1.0	NR	55.0/55.6	46.0/47.3	Phase III, double-blind, parallel-group, RCT, in 74 centres in 4 countries	5	Saxagliptin vs. placebo	None	2.5, 5	76
Rosenstock 2013 [571] NCT00121641	T2DM (*n*=467)	2.7±3.4/2.3±2.7	8.6±0.9/7.9±0.9	NR	53.3/53.9	51.2/49.5	Phase III, double-blind, open-label saxagliptin (10mg/d), parallel-group, RCT, in 135 centres in 6 countries, study 11	5	Saxagliptin vs. placebo	None	2.5, 5, 10	53
DeFronzo 2013 [571] NCT00121667	T2DM (*n*=743)	6.4±5.5/6.7±0.9	8.0±5.6/8.1±0.9	NR	54.5/54.8	49.7/53.6	Phase III, double-blind, parallel-group, RCT, in 154 centres in 9 countries, study 14	4	Saxagliptin vs. placebo	Metformin	2.5, 5, 10	206
Yang 2011 [572] NCT00661362	T2DM (*n*=570)	5.1±5.0/5.1±4.0	7.9±0.8/7.9±0.8	NR	53.8/54.4	48.1/48.4	Phase III, double-blind, parallel-group, RCT, in Asian patients	2	Saxagliptin vs. placebo	Metformin	5	24
Stenlöf 2010 [573] NCT00683657	T2DM (*n*=93)	NR	NR	NR	54.5/55.8	56.5/49.0	Phase III, double-blind, parallel-group, RCT, 27 centres in 8 countries	2	Saxagliptin vs. placebo	Metformin	5	4
White 2014 [574] NCT00885378	T2DM (*n*=160)	5.8±6.4/6.2±4.2	7.9±0.9/7.9±0.8	NR	54.0/56.6	54.1/52.3	Phase III, double-blind, parallel-group, RCT, 41 centres in 4 countries	2	Saxagliptin vs. placebo	Metformin	5	12
Chacra 2011 [575] NCT00313313	T2DM (*n*=768)	6.9±5.8/6.8±5.7	8.4±0.9/8.4±0.9	NR	55.1/55.1	44.6/46.1	Phase III, double-blind, parallel-group, RCT, in 115 centres in 13 countries	3	Saxagliptin vs. placebo	Glyburide	2.5, 5	76
Nowicki 2011 [576] NCT00614939	T2DM with CKD[e] (*n*=170)	15.1±7.5/18.2±8.5	8.5±1.2/8.1±1.1	NR	66.8/66.2	37.6/48.2	Phase III, double-blind, parallel-group, RCT, in 75 centres in 14 countries	2	Saxagliptin vs. placebo	Glinide ± sulfonylurea ± TZDs ± α-glucosidase-Is + insulin	2.5	52
Hollander 2011 [518] NCT00295633	T2DM (*n*=565)	5.2±5.1/5.1±5.4	8.3±1.1/8.2±1.1	NR	54.1/54.0	51.1/46.2	Phase III, double-blind, parallel-group, RCT, in 133 centres in 8 countries	3	Saxagliptin vs. placebo	TZDs (pioglitazone + rosiglitazone)	2.5, 5	76

Barnett 2012 [577] NCT00757588	T2DM (*n*=455)	11.8±6.9/12.2±7.3	8.7±0.9/8.6±0.8	NR	57.2/57.3	40.0/45.0	Phase III, double-blind, parallel-group, RCT, in 80 centres in 10 countries	2	Saxagliptin vs. placebo	Insulin ± metformin	5	52
Scirica 2013 [390] NCT01107886	T2DM with CVD or CRF[b] (*n*=16,492)	10.3±2.8/10.3±2.8	8.0±1.4/8.0±1.4[**]	NR	65.1/65.0	66.6/67.3	Phase IV, double-blind, parallel-group, RCT, in 788 centres in 26 countries, SAVOR–TIMI 53	2	Saxagliptin vs. placebo	None + metformin + sulfonylurea + TZDs +insulin + other AHGs	2.5, 5	109
Henry 2011 [578] NCT00374907	T2DM (*n*=36)	2.7±4.4/3.7±4.0	6.9±0.5/6.6±0.6	NR	58.0/55.0	40.0/37.5	Phase III, double-blind, parallel-group, RCT, 3 centres in USA	2	Saxagliptin vs. placebo + metformin	None	5	116
Jadzinsky 2009 Pfützner 2011 [579] NCT00327015	T2DM (*n*=1306)	1.7±2.9/1.7±3.1	9.5±1.2/9.4±1.3	NR	52.1/51.8	49.1/49.7	Phase III, double-blind, parallel-group, RCT, 211 centres in 13 countries	4	Saxagliptin vs. metformin	Metformin	5-10	76
Hermans 2012 [580] NCT01006590	T2DM (*n*=286)	6.0±5.3/6.9±6.0	7.7±0.9/7.8±0.8	NR	58.7/58.6	59.9/54.7	Phase III, double-blind, parallel-group, RCT, 50 centres in 7 countries, PROMPT trial	2	Saxagliptin vs. metformin	Metformin	5	24
Neutel 2013 [581] NCT00918138	T2DM (*n*=93)	6.2±4.5/5.1± 3.9	8.6±0.9/8.4± 0.9	NR	53.9/50.6	45.7/53.2	Phase III, double-blind, parallel-group, RCT, 21 centres in 4 countries	2	Saxagliptin vs. metformin	Metformin	5	4
Fonseca 2012 [582] NCT00960076	T2DM (*n*=282)	6.5±5.4/5.9±5.2	8.4±0.9/8.3±0.9	NR	55.2/55.5	41.3/50.7	Phase IIIb, double-blind, parallel-group, RCT, 35 centres in 5 countries,	2	Saxagliptin vs. metformin	Metformin	5	18
Göke 2013 [583] NCT00575588	T2DM (*n*=858)	5.5±4.5/5.5±4.7	7.7±0.9/7.7±0.9	NR	57.5/57.6	49.5/54.0	Phase III, double-blind, parallel-group, RCT, in 95 centres in 11 countries	2	Saxagliptin vs glipizide	Metformin	5	104
Schernthaner 2015 [584] NCT01006603	T2DM (*n*=718)	7.6±6.4/7.6±6.0	7.6±0.7/7.6±0.7	CVA 19 (5.3%) vs. 21 (5.8%)	72.5/72.7	60.3/63.3	Phase IIIb/IV, double-blind, parallel-group, RCT, in 131 centres in 13 countries	2	Saxagliptin vs. glimepiride	Metformin	5	52
Scheen 2010 [585] NCT00666458	T2DM (*n*=801)	6.3±5.0/6.3±4.7	7.7±0.1/7.7±0.0[‡]	NR	58.8/58.1	47.1/50.8	Phase IIIb, double-blind, parallel-group, RCT, 86 centres in 9 countries	2	Saxagliptin vs. sitagliptin	Metformin	Saxagliptin 5 Sitagliptin 100	18
Sitagliptin therapy												
Hage 2014 [586] NCT00627744	T2DM or IGT with ACS (*n*=71)	IGT=24.0±7.1/23.0±62.0 T2DM=10.0±29.0/14.0±38.0	6.8/6.8	Stroke/TIA 2 (6.0%) vs. 3 (8.0%)	69.0/66.0	85.0/78.0	Phase IV, double-blind, parallel-group, RCT, In Sweden, BEGAMI study	2	Sitagliptin vs. placebo	None	100	12
Mohan 2009 [587] NCT00289848	T2DM (*n*=530)	2.1±1.7/8.7±1.0	1.9±1.6/8.8±1.1	NR	51.0/51.0	56.8/59.6	Phase III, double-blind, parallel-group, RCT, in 3 countries	2	Sitagliptin vs. placebo	None	100	18
Barzilai 2011 [588] NCT00305604	T2DM (*n*=206)	7.2±35/7.0±47	7.8±10/7.8±9.7	NR	71.6/72.1	47.1/47.1	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	None	50-100	24
Ji 2016 [589] NCT01076088	T2DM (*n*=744)	1.1±0.3/1.1±0.2	NR	NR	53.0/53.0	75.0/61.2	Phase III, double-blind, parallel-group, RCT, in China	6	Sitagliptin vs. placebo	None	50-100	24
Scott 2007 [590] NCT00482079	T2DM (*n*=620)	NR	NR	NR	NR	NR	Phase II, double-blind, parallel-group, RCT	6	Sitagliptin vs. placebo	None	NR	21
HU 2015 [591] NCT01289990	T2DM (*n*=446)	≤1->10/≤1->10	8.1±0.8/8.2±0.8	NR	55.1/55.6	63.2/51.0	Phase III, parallel-group, RCT, in 69 centres in 8 countries	2	Sitagliptin vs. placebo	None	100	76
Aschner 2006 [592] NCT00087516	T2DM (*n*=741)	NR	8.0±0.9/8.0±0.8	NR	54.2/54.3	52.0/51.4	Double-blind, parallel-group, RCT	3	Sitagliptin vs. placebo	None	100-200	24
Roden 2013 [593] NCT01177813	T2DM (*n*=452)	≤1->10/≤1->10	7·9±0·8/7·9±0·8	NR	53.4/55.0	67.2/58.6	Phase III, double-blind, parallel-group RCT, in 124 centres in 9 countries	2	Sitagliptin vs. placebo	None	100	24
Hanefeld 2007 [594] NCT00481663	T2DM (*n*=552)	NR	NR	NR	NR	NR	Phase II, double-blind, parallel-group, RCT	5	Sitagliptin vs. placebo	NR	25-50-100	12
Wang 2017 [595] NCT01177384	T2DM (*n*=380)	7.4±4.9/8.2±5.7	8.1±0.8/8.1±0.9	NR	56.5/57.8	50.8/51.3	Phase III, double-blind, parallel-group, RCT, in India	2	Sitagliptin vs. placebo	Acarbose (glucobay)	100	24
Yang 2012 [596] NCT00813995	T2DM (*n*=395)	NR	8.5±0.9/8.5±0.9	NR	54.1/55.1	46.7/54.5	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Metformin	100	24
Raz 2008 [597] NCT00337610	T2DM (*n*=190)	NR	9.3±0.9/9.1±0.8	NR	53.6/56.1	51.0/41.5	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Metformin	100	30
NCT00420511 [598]	T2DM (*n*=21)	2.8±4.0/3.5±8.0	6.2±6.9/6.1±6.9	NR	61.3/60.8	60.0/72.7	Phase II, double-blind, parallel-group, RCT, in Canada, BEST trial	2	Sitagliptin vs. placebo	Metformin	100	48
Bergenstal 2012 [599] NCT00754988	T2DM (*n*=274)	6.0±5.0/5.5±3.9	7.9±0.9/8.0±0.8	NR	55.5/56.1	59.3/52.2	Phase III, double-blind, parallel-group RCT in 149 centres in 23 countries, T-Emerge 4 trials	2	Sitagliptin vs. placebo	Metformin	100	156

Gadde 2017 [600] NCT01652729	T2DM (*n*=183)	7.9±4.6/8.7±5.8	8.5±1.0/8.5±1.0	NR	53.4/54.3	60.7/54.1	Phase III, open-label, parallel-group, RCT, in 60 centres in USA, DURATION-NEO-2 trial	2	Sitagliptin vs. placebo	Metformin	100	28
Rosenstock 2012 [601] NCT00642278	T2DM (*n*=130)	6.0±4.9/6.4±5.0	7.6±0.9/7.8±0.8	NR	53.1/52.5	51.0/53.1	Phase II, double-blind, parallel-group RCT, in 85 centres in 13 countries	2	Sitagliptin vs. placebo	Metformin	100	12
Rosenstock 2013 [602] NCT00749190	T2DM (*n*=51)	NR	8.0±0.7/8.1±0.9	NR	58.1/58.7	50.7/50.0	Phase II, open-label parallel-group RCT, in 116 centres in 16 countries	2	Sitagliptin vs. placebo	Metformin	100	12
Ba 2017 [603] NCT01590771	T2DM (*n*=497)	7.1±5.4/6.9±4.9	8.6±1.1/8.5±0.9	NR	57.5/56.5	47.0/53.0	Phase III, double-blind, parallel-group, RCT, in China	2	Sitagliptin vs. placebo	Metformin ± sulfonylurea	100	24
Dobs 2013 [604] NCT00350779	T2DM (*n*=262)	9.3±5.9/9.4±6.8	8.8±1.0/8.7±1.0	NR	54.4/54.8	56.0/60.0	Double-blind, parallel-group, RCT, in 41 centres in USA, Europe and Asia	2	Sitagliptin vs. placebo	Rosiglitazone + metformin	100	77
Fonseca 2013 [511] NCT00885352	T2DM (*n*=313)	9.4±5.8/10.2±6.1	8.8±1.0/8.7±1.0	NR	55.7/65.4	61.8/62.8	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Metformin + pioglitazone	100	26
Rosenstock 2006 [510] NCT00086502	T2DM (*n*=353)	6.1±5.4/6.1±5.7	8.1±0.8/8.0±0.8	NR	55.6/56.9	53.1/57.9	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Pioglitazone	100	24
Green 2015 [391] NCT00790205	T2DM with established CVD (*n*=14,523)	11.6±8.1/7.2±0.5	11.6±8.1/7.2±0.5	CVD 1806 (24.6%) 1782 (42.3%)	65.4/65.5	70.9/70.5	Double-blind, parallel-group, RCT, in 673 centres in 38 countries, TECOS trial	2	Sitagliptin vs. placebo	Metformin + sulfonylurea + TZDs +insulin	50, 100	157**
Shankar 2017 [605] NCT01590797	T2DM (*n*=467)	11.0±5.0/11.3±5.8	8.7±0.9/8.8±0.9	NR	58.6/56.7	65.6/49.8	Phase III, double-blind, parallel-group, RCT, in China	2	Sitagliptin vs. placebo	± Metformin + insulin	100	24
Vilsbøll 2010 [606] NCT00395343	T2DM (*n*=641)	13.0±7.0/12.0±6.0	<8%-≥9%/<8%-≥9%	NR	58.3/57.2	48.8/53.0	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Insulin ± metformin	100	24
Mathieu 2015 [607] NCT01462266	T2DM (*n*=658)	13.2±6.0/13.7±6.4	8.7±1.0/8.8±1.0	NR	59.3/58.3	45.9/49.8	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo	Insulin ± metformin	100	24
Williams-Herman 2010 [608] NCT00103857	T2DM (*n*=1208)	5.9±6.7/5.9±6.9	8.6±1.0/8.6±0.9	NR	53.3/53.4	51.7/48.9	Phase III, double-blind, factorial design RCT	7	Sitagliptin vs. placebo + metformin	Metformin	100	104
Amin 2015 [609] NCT01059825	T2DM + hypertension (*n*=484)	6.4±0.9/6.4±0.9	8.2±0.1/8.2±0.1	NR	55.0/55.1	72.7/63.2	Phase II, double-blind, parallel-group, RCT	3	Sitagliptin vs. placebo + metformin	AHG agents	100	12
Aschner 2010 [610] NCT00449930	T2DM (*n*=1050)	2.6±3.9/2.1±3.5	7.2±0.7/7.3±0.7	NR	56.0/56.0	47.3/44.8	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. metformin	None	100	24
Olansky 2011 [611] NCT00482729	T2DM (*n*=1246)	NR	9.9±1.8/9.8±1.8	NR	49.4/50.0	56.5/57.2	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin/metformin§ vs. metformin	None	100-200	44
Perez-Monteverde 2011 [612] NCT00541450	T2DM (*n*=472)	2.9±2.8/ 3.5±3.7	9.0±1.4/9.1±1.4	NR	50.5/51.7	62.3/59.7	Phase III, parallel placebo-controlled trial	2	Sitagliptin/metformin§ vs. pioglitazone	None	100-200	40
Wainstein 2012 [487] NCT00532935	T2DM (*n*=517)	3.2±4.0/3.3±3.5	9.0±1.3/8.9±1.3	NR	52.4/52.2	54.8/52.3	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin/metformin§ vs. pioglitazone	None	100-200	32
Russel-Jones 2012 [613] NCT00676338	T2DM (*n*=572)	2.7±3.7/2.7±3.7	8.5±1.3/8.6±1.2	NR	52.3/54.5	56.0/59.6	Phase III, double-blind, parallel-group, RCT, in 106 centres in 22 countries, DURATION-4 trial	3	Sitagliptin vs. metformin + pioglitazone	None	100	36
Raz 2006 [614] NCT00094757	T2DM (*n*=521)	4.5±4.1/4.7±5.0	8.1±0.9/8.1±0.9	NR	55.0/55.5	52.1/62.7	Double-blind, parallel-group, RCT, multinational	3	Sitagliptin vs. placebo + pioglitazone	None	100-200	54
NCT01076075 [509]	T2DM (*n*=422)	NR	8.4±0.8/8.4±0.9	NR	54.4/55.4	45.2/46.2	Phase III, parallel-group, RCT, in 161 centres in 23 countries	2	Sitagliptin vs. placebo + pioglitazone	Metformin + sulfonylurea	100	54
Hermansen 2007 [615] NCT00106704	T2DM (*n*=441)	8.3±5.3/9.3±6.7	8.3±0.7/8.3±0.7	NR	55.6/56.5	52.7/53.4	Double-blind, crossover RCT, multinational	2	Sitagliptin vs. placebo + pioglitazone	± Metformin + glimepiride	100	24
Yoon 2012 [507] NCT01028391	T2DM (*n*=317)	2.6±4.0/9.4±1.1	1.6±3.7/9.4±1.4	NR	51.4/52.3	52.4/58.8	Double-blind, parallel-group, RCT, in 28 centres in 15 countries	2	Sitagliptin vs. pioglitazone	Pioglitazone	100	54
Yoon 2011 [507] NCT00397631	T2DM (*n*=317)	2.6±4.0/1.6±3.7	7.0±1.2/7.6±1.2	NR	50.2/51.6	52.5/56.0	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin + pioglitazone vs. pioglitazone	NR	100	54
Bergenstal 2010 [616] NCT00637273	T2DM (*n*=497)	5.0±4.0/6.0±5.0	8·5±1·2/8·5±1·1	NR	52.7/52.2	51.8/51.8	Phase III, double-blind, parallel-group, RCT, in 62 centres in USA, Mexico and India, DURATION-2 trial	2	sitagliptin vs. pioglitazone	Metformin	100	26
NCT00722371 [474]	T2DM (*n*=1615)	NR	NR	NR	57.0/57.3	56.8/56.0	Phase III, double-blind, parallel-group, RCT	7	Sitagliptin vs. pioglitazone	Metformin + sulfonylurea	100	54
Chan 2008 [617] NCT00095056	T2DM with CKD (*n*=91)	3.6±9.7/13.2±8.9	7.6±0.9/7.8±0.9	NR	68.9/65.3	47.7/61.5	Phase III, double-blind, parallel-group, RCT, in 69 centres in 11 countries	2	Sitagliptin vs. placebo + glipizide	None	25	54

Charbonnel 2006 [512] NCT00086515	T2DM (*n*=701)	NR	7.96±0.8/8.0±0.8	NR	54.4/54.7	55.8/59.5	Double-blind, parallel-group, RCT	2	Sitagliptin vs. placebo + glipizide	Metformin	100	24
Ahrén 2014 [618] NCT00838903	T2DM (*n*=710)	5.8±4.8/6.7±6.6	8.1±0.8/8.2±0.9	NR	54.3/56.1	46.0/49.5	Phase III, double-blind, parallel-group, RCT, in 289 centres in 10 countries, HARMONY 3 trial	3	Sitagliptin vs. placebo + glimepiride	Metformin	100	104
Arjona Ferreira 2013 [619] NCT00509236	T2DM with CKD on dialysis (*n*=129)	19±6.0/16±6.0	7.9±0.7/7.8±0.7	NR	60.5/58.5	62.5/56.9	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. glipizide	NR	25	54
Ferreira 2013 [620] NCT00509262	T2DM with CKD (*n*=422)	10.7±7.5/10.1±7.8	7.8±0.7/7.8±0.7	NR	64.2/64.2	62.1/57.5	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. glipizide	NR	25-50	54
Seck 2010 [621] NCT00094770	T2DM (*n*=1172)	5.8±5.7/5.7±4.9	7.3±0.6/7.3±0.7	NR	56.8/56.6	57.1/61.3	Double-blind, parallel-group, RCT	2	Sitagliptin vs. glipizide	Metformin	100	52
Arechavaleta 2011 [622] NCT00701090	T2DM (*n*=1034)	6.8±4.6/6.7±4.8	7.5±0.7/7.5±0.8	NR	56.3/56.2	55.0/53.8	Phase III, double-blind, parallel-group, RCT	2	Sitagliptin vs. glimepiride	Metformin	100	30
NCT01131182 [623]	T2DM (*n*=1021)	NR	NR	NR	55.0/55.0	53.1/49.6	Open-label, parallel-group, RCT	2	Sitagliptin vs. sulfonylurea	Metformin	100	4
Terauchi 2017 [624] NCT01183104	T2DM (*n*=291)	NR	7.5±0.7/7.5±0.7	NR	70.2/70.8	51.7/61.2	Open-label, RCT, parallel-group, in Japan, START-J trial	2	Sitagliptin vs. glimepiride	None ± α-glucosidase-Is ± biguanide	50	52
Leiter 2014 [625] NCT01098539	T2DM with CKD (*n*=495)	11.6±8.5/10.8±7.4	8.2±0.9/8.1±1.0	NR	63.2/63.5	54.6/52.8	Phase III, double-blind, parallel-group, RCT, Harmony 8 trial	2	Sitagliptin vs. albiglutide	± AHG agents	Sitagliptin 30-50 Albiglutide 30-50	52
Pratley 2011 [626] NCT00700817	T2DM (*n*=658)	6.3±5.4/6.2±4.9	NR	NR	55.0/55.5	54.8/52.1	Phase III, double-blind, parallel-group, RCT, in 166 centres in 13 countries	3	Sitagliptin vs. liraglutide	Metformin	Sitagliptin 100 Liraglutide 1.2-1.8	78
Zang 2016 [627] NCT02008682	T2DM (*n*=367)	5.2±5.4/5.3±4.4	8.1±0.8/8.1±0.8	NR	51.4/51.7	63.6/55.7	Phase IV, parallel-group, open-label RCT, in 10 centres in China	2	Sitagliptin vs. liraglutide	Metformin	Sitagliptin 100 Liraglutide 1.8	26
NCT01519674 [628]	T2DM (*n*=575)	NR	8.4±0.8/8.4±0.8	NR	56.0/54.8	48.9/57.2	Phase IV, open-label, parallel-group, RCT, in 69 centres in 10 countries	3	Sitagliptin + biphasic insulin aspart vs. biphasic insulin aspart	Metformin	100-200	24
Philis-Tsimikas 2013 [515] NCT01046110	T2DM (*n*=454)	7.7±5.9/7.8±6.2	9.0±1.0/8.8±1.0	NR	54.9/56.4	54.5/62.7	Phase III, open-label, parallel-group, RCT, in 93 centres in 7 countries	2	Sitagliptin vs. insulin degludec	Metformin, sulfonylurea, glindes, pioglitazone	100	26
NCT00875394 [629]	T2DM (*n*=68)	8.9±7.1/6.8±8.5	8.8±1.5/8.0±1.8	NR	54.2/54.7	30.6/25.4	Phase III, open-label, parallel-group, RCT	3	Sitagliptin vs. any AHGs agents other DPP4-Is	Metformin	100	24
Vildagliptin therapy												
NCT00646542 [630]	T2DM with CKD (*n*=519)	NR	NR	NR	NR	NR	Phase III, double-blind, parallel-group, RCT, in 12 countries	2	Vildagliptin vs. placebo	None	50	52
NCT00821977 [631]	T2DM (*n*=451)	NR	NR	NR	NR	NR	Phase II/III, double-blind, parallel-group, RCT, in 176 centres in 8 countries	3	Vildagliptin vs. placebo	None	NR	76
Scherbaum 2008 [632] NCT00300287	T2DM (*n*=306)	2.1±2.1/2.5±2.6	6.6±0.4/6.7±0.4	NR	63.3/62.8	59.6/59.3	Phase III, double-blind, parallel-group, RCT	2	Vildagliptin vs. placebo	None	50	52
Dejager 2007 [633] NCT00099905	T2DM (*n*=632)	NR	NR	NR	53.0/53.0	NR	Phase III, double-blind, parallel-group, RCT, in USA	4	Vildagliptin vs. placebo	None	50, 100	24
McMurray 2013 [634] NCT00894868	T2DM with CHF class I-III (*n*=254)	9.5±8.1/9.1±7.8	7.8±0.9/7.8±1.1	Stroke 12 (9.4%) vs. 11 (8.7%)	63.0/63.4	76.0/70.0	Phase IV, double-blind, parallel-group, RCT in 94 centres in 15 countries, VIVIDD trial	2	Vildagliptin vs. placebo	None	100	52
Pan 2012 [635] NCT00822211	T2DM (*n*=438)	4.9±4.6/5.2±4.6	8.1±0.8/8.0±0.8	NR	53.9/54.5	27.0/18.0	Double-blind, parallel-group, RCT, in China	3	Vildagliptin vs. placebo	Metformin	50, 100	24
CLAF237ADE02 [636]	T2DM (*n*=402)	NR	NR	NR	61.0/61.0	59.4/53.1	Double-blind, parallel-group, RCT	2	Vildagliptin vs. placebo	Metformin	50, 100	24
Bosi 2007 [637] NCT00099892	T2DM (*n*=541)	6.3±5.1/8.4±1.0	6.2±5.3/8.3±0.9	NR	54.1/54.5	59.4/53.1	Phase III, double-blind, parallel-group, RCT, 109 centres in 4 countries	3	Vildagliptin vs. placebo	Metformin	50, 100	24
Yang 2015 [638] NCT01357252	T2DM (*n*=278)	6.9±4.6/7.0±10.0	6.9±4.1/7.2±11.0	NR	58.3/58.7	55.2/58.1	Double-blind, parallel-group, RCT, in China	2	Vildagliptin vs. placebo	Sulfonylurea	50	24
Garber 2008 [639] NCT00099944	T2DM (*n*=515)	6.8±5.3/7.8±5.8	8.5±0.9/8.5±1.0	NR	58.4/57.9	59.5/58.3	Phase III, double-blind, parallel-group, RCT, in 12 countries	3	Vildagliptin vs. placebo	Sulfonylurea	50-100	24

Fonseca 2009 [640] NCT00099931	T2DM (*n*=296)	14.4±8.6/14.9±8.4	8.4±1.0/8.4±1.1	NR	59.6/58.9	47.9/54.6	Phase III, double-blind, parallel-group, RCT, in 68 centres 10 in Germany, 5 Finland, 4 Spain and 49 USA	2	Vildagliptin vs. placebo	Insulin	100	24
Bosi 2009 [641] NCT00468039	T2DM (*n*=1171)	23.7±35.2/6.3±39.9	8.7±1.0/8.6±0.9	NR	44.4/52.4	58.4/58.2	Phase III, open-label trial, in 250 centres in USA, Canada and India	4	Vildagliptin vs. placebo + metformin	None	50-100	24
Schweizer 2007 [642] NCT00099866	T2DM (*n*=760)	1.1±3.5/1.0±3.3[**]	8.7±1.1/8.7±1.1	NR	52.8/53.6	52.9/57.5	Phase III, double-blind, parallel-group, RCT, in 183 centres in 10 countries, CLAF237A2309E1 trial	2	Vildagliptin vs. metformin	None	100	104
Pan 2008 [643] NCT00110240	T2DM (*n*=660)	1.2±2.4/1.3±2.4	8.6±0.9/8.6±1.0	NR	51.8/51.9	60.1/63.2	Phase III, double-blind, parallel-group, RCT, in 31 centres in China, Romania and Spain	2	Vildagliptin vs. α-glucosidase-Is (acarbose)	None	100	24
Rosenstock 2009 [644] NCT00138619	T2DM (*n*=591)	2.3±3.4/2.7±4.2	8.7±1.1/8.7±1.1	NR	54.5/54.2	57.5/57.6	Phase III, double-blind, parallel-group, RCT, in 202 centres in 11 countries in USA and Europe	2	Vildagliptin vs. rosiglitazone	None	100	104
Bolli 2009 [645] NCT00237237	T2DM (*n*=575)	6.4±4.9/6.4±5.2	8.4±1.0/8.4±0.9	NR	56.3/57.0	61.7/64.1	Double-blind, parallel-group, RCT, in USA and Germany	2	Vildagliptin vs. pioglitazone	Metformin	100	52
Foley 2009 [646] NCT00102388	T2DM (*n*=1092)	NR	NR	NR	55.2/54.3	58.8/52.7	Double-blind, parallel-group, RCT	2	Vildagliptin vs. gliclazide	None	100	104
Ferrannini 2009 [647] NCT00106340	T2DM (*n*=2772)	5.7±5.2/5.8±5.0	7.3±0.7/7.3±0.7	NR	57.5/57.5	52.8/54.1	Double-blind, parallel-group, RCT, in USA and Germany	2	Vildagliptin vs. glimepiride	Metformin	100	52

Abbreviations: *ACS*, acute coronary syndrome; *ACE*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptors blocker; *AHG*, anti-hyperglycaemic drugs; *CVA*, cardiovascular accident; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease; C*RF*, chronic renal failure; *CHF*, congestive heart failure; *IGT*, impaired glucose tolerance; *mμ/d*, microgram pear day; *mg/d*, milligram pear day; NR, not report; *RCT*, randomised controlled trial; *TZDs*, thiazolidinedione; *T2DM*, type 2 diabetes mellitus.

Note: [‡] Mean age and dosages present for intervention drugs; [**]Median age; [**]Median year; [**]Median (interquartile range); [¶]Novel treatment of fixed-dose combination of 2 different classes of AHG; †values are expressed as mean ± SD or [ŧ]mean ± SE.

[a] 25 mg in patients with an estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1.73 m^2 of body surface area; 12.5 mg with an eGFR of 30 to<60 ml/min/1.73 m^2; and 6.25 mg with an eGFR of<30 ml/min/1.73 m^2.

[b] or 50 mg daily if the baseline eGFR was ≥30 and<50 ml/min/1.73 m^2.

[c] 2.5 mg daily in patients with an eGFR ≤50 ml/min/1.73 m^2.

[d] <30 ml/min/1.73 m^2 not on chronic dialysis.

[e] Degree of renal impairment: moderate (CrCl ≥30 and <50 ml⁄min), severe (CrCl <30 ml⁄min and not receiving dialysis) or end-stage renal disease (ESRD) on haemodialysis.

3.5.2 GLPA-As therapies

Supplemental Table 3-5. Baseline characteristics of GLP1-RAs therapies included trials

Study Trial registry	Population Sample size	T2DM† Mean duration (years)	HbA1C levels %	Prior stroke / TIA (*n*., %)	Mean age (years)‡	Males (%)	Study design and country	Parallel arms	GLP1-RAs vs. comparators	Background AHGs therapy	GLP1-RAs dosage‡	Duration (weeks)
Albiglutide therapy												
Nauck 2016 [648] NCT00849017	T2DM (*n*=301)	3.8±3.9/4.3±4.0	8.1±0.9/8.0±0.9	NR	52.8/53.1	53.9/57.4	Phase III, open-label, parallel-group, RCT, in 262 centres in 3 countries	3	Albiglutide vs. placebo	None	30-50 mg/week	156
Hernandez 2018 [392] NCT02465515	T2DM and CVD (*n*=9463)	14.1±8.6/7.9±6.1	8.7±1.5/8.7±1.5	Stroke=827 (17%) vs. 854 (18%)	64.1/64.2	70.0/69.0	Phase III, double-blind, parallel-group, RCT, in 610 centres in 28 countries, HARMONY Outcomes trial	2	Albiglutide vs. placebo	AHG agents	30-50 mg/week	84**
Reusch 2014 [649] NCT00849056	T2DM (*n*=301)	8.0±5.6/7.9±6.1	8.1±1.0/8.1±0.9	NR	55.2/54.9	61.3/58.3	Phase III, double-blind, parallel-group, RCT, in 331 centres in 6 countries, HARMONY 1	2	Albiglutide vs. placebo	Pioglitazone ± metformin	30 mg/week	156
Nauck 2016 [648] NCT00839527	T2DM (*n*=301)	3.8±4.2/4.3±4.0	8.1±0.8/8.0±0.9	NR	52.8/53.1	53.9/57.4	Phase III, double-blind, parallel-group, RCT, in 143 centres USA and Mexico, HARMONY 2	3	Albiglutide vs. placebo	Metformin + insulin preferred	30-50 mg/week	156
Seino 2014 [650] NCT01098461	T2DM (*n*=301)	7.1±5.2/6.7±7.8	< or ≥ 8.4/< or ≥ 8.4	NR	56.8/57.5	69.7/69.8	Phase II, double-blind, parallel-group, RCT, in 30 centres in Japan	4	Albiglutide vs. placebo	Insulin	30-50 mg/week	24
Ahrén 2017 [618] NCT00838903	T2DM (*n*=710)	6.0±4.3/6.7±6.6	8.1±0.8/8.2±0.9	NR	54.3/56.1	44.7/49.5	Phase III, double-blind RCT, HARMONY-3	3	Albiglutide vs. placebo + glimepiride	± AHG agents	30 mg/week	156
Home 2014 [472] NCT00839527	T2DM (*n*=663)	8.5±6.3/9.2±6.1	8.2±0.9/8.2±0.9	NR	54.5/55.7	49.8/57.2	Phase III, double-blind, parallel-group, RCT, in 234 centres in 9 countries, HARMONY 5	3	Albiglutide vs. placebo + pioglitazone	Metformin + glimepiride	30 mg/week	156
Pratley 2014 [651] NCT01128894	T2DM (*n*=812)	8·4±6·1/8·3±5·6	8·2±0·9/15±0·8	NR	55.4/55.8	47.3/53.4	Phase III, open-label, parallel-group, RCT, in 174 centres in 8 countries, HARMONY 7	2	Albiglutide vs. liraglutide	Metformin ± sulfonylurea ± TZDs	Albiglutide 50 mg/d Liraglutide 1.8 mg/d	32
Weissman 2014 [652] NCT00838916	T2DM (*n*=745)	8.9±6.5/8.4±5.7	8.3±0.9/8.4±0.9	NR	55.8/54.7	56.7/54.8	Phase III, open-label, parallel-group, RCT, in 338 centres in 4 countries, HARMONY 4	2	Albiglutide vs. insulin glargine	Metformin ± sulfonylurea	30 mg/week	156
Rosenstock 2014 [653] NCT00976391	T2DM (*n*=566)	11.0±7.0/11.0±6.0	8.5±0.9/8.4±0.9	NR	54.8/56.3	46.0/48.0	Phase III, open-label, parallel-group, RCT, HARMONY 6	2	Albiglutide vs. insulin lispro	Metformin ± pioglitazone ± α-glucosidase-Is	50 mg/d	52
Dulaglutide therapy												
Gerstein 2019 [400] NCT01394952	T2DM with CVD (*n*=9622)	9.5 (5.5-14.5)/9.5 (5.5-14.5)	7.3±1.1/7.4±1.1	NR	66.2/66.2	53.4/53.9	Phase III, double-blind, RCT, in 320 centres in 26 countries, REWIND trial	2	Dulaglitude vs. placebo	NR	1.5 mg/d	339
Wysham 2014 [523] NCT01064687	T2DM (*n*=700)	9.0±6.0/9.0±6.0	8.1±1.3/8.1±1.3	NR	54.6/56.0	58.8/59.2	Phase III, double-blind, parallel-group, RCT, in 89 centres in 4 countries, AWARD-1 trial	2	Dulaglutide vs. placebo	Metformin + pioglitazone	0.75-1.5mg/d	52
Pozzilli 2017 [654] NCT02152371	T2DM (*n*=300)	13.0±7.5/13.3±7.7	8.4±0.9/8.3±0.8	NR	60.2/60.6	56.6/58.6	Phase III, double-blind, parallel-group, RCT, in 40 centres in 7 countries, AWARD-9 trial	2	Dulaglutide vs. placebo	Basal insulin glargine ± metformin	1.5 mg/d	28
Exenatide therapy												
Holman 2017 [393] NCT01144338	T2DM ± CVD (*n*=14752)	12.0(7.0-18.0)/12.0(7.0-18.0)**	8.0(7.3-8.9)/8.0(7.3-8.9)**	NR	63.0/63.0**	62.0/62.0	Double-blind, parallel-group, RCT, in 687 centres in 35 countries. EXSCEL trial	2	Exenatide vs. placebo	Metformin ± sulfonylurea ± DPP4-Is	2 mg/week	167**
Gao 2009 [655] NCT00324363	T2DM (*n*=466)	8.0±6.0/8.0±5.0	8.3±1.0/8.3±1.0	NR	55.0/54.0	48.0/41.0	Double-blind, parallel-group, RCT, in 4 countries	2	Exenatide vs. placebo	Metformin ± sulfonylurea	10-20 µg/d	16
Gill 2010 [656] NCT00516074	T2DM (*n*=54)	7.0±4.0/6.0±4.0	7.5±0.9/7.1±0.7	NR	57.0/54.0	68.0/42.0	Double-blind, parallel-group RCT, in Canada and Netherlands	2	Exenatide vs. placebo	Metformin ± TZDs	5-10 µg/d	12
NCT00603239 [657]	T2DM (*n*=165)	NR	NR	NR	54.9/54.1	60.3/57.4	Phase III, double-blind, parallel-group, RCT, in 25 centres in 5 countries	2	Exenatide vs. placebo	Metformin + TZDs	10-20 µg/week	26

Wysham 2014 [523] NCT01064687	T2DM (*n*=417)	9.0±6.0/9.0±6.0	8.1±1.3/8.1±1.3	NR	55.5/56.0	56.5/59.2	Phase III, double-blind, parallel-group, RCT, in 89 centres in 4 countries, AWARD-1 trial	2	Exenatide vs. placebo	Metformin + pioglitazone	10-20 µg/d	52
Gadde 2017 [600] NCT01652729	T2DM (*n*=242)	8.5±6.3/8.7±5.8	8.4±0.9/8.5±1.0	NR	53.4/54.3	49.2/54.1	Phase III, open-label, parallel-group, RCT, in 60 centres in USA, DURATION-NEO-2 trial	2	Exenatide vs. placebo	Metformin	2 mg/d	28
Gallwitz 2012 [658] NCT00359762	T2DM (*n*=1335)	5·8±4·8/5·5±4·3	7·5±0·7/7·4±0·7	NR	56.1/56.8	55.5/51.7	Phase III, open-label, parallel-group, RCT, in 128 centres in 14 countries, EUREXA trial	4	Exenatide vs. glimepiride	Metformin	10-50 µg/d	235
Buse 2013 [659] NCT01029886	T2DM (*n*=911)	8.0±6.0/9.0±6.0	8·5±1·0/8·4±1·0	NR	56.6/56.7	55.1/54.4	Phase III, open-label, parallel-group, RCT, in 110 centres in 21 countries, DURATION-6	2	Exenatide vs. liraglutide	Metformin ± sulfonylurea ± pioglitazone	Exenatide 2 mg/week Liraglutide 1.8 mg/d	26
Russel-Jones 2012 [613] NCT00676338	T2DM (*n*=657)	2.7±3.2/2.7±3.7	8.5±1.2/8.6±1.2	NR	53.7/54.5	56.0/61.1	Phase III, double-blind, parallel-group, RCT, in 106 centres in 22 countries, DURATION-4 trial	3	Exenatide vs. metformin + pioglitazone	None	2 mg/week	36
Bergenstal 2010 [616] NCT00637273	T2DM (*n*=497)	6.0±5.0/6.0±5.0	8·6±1·2/8·5±1·1	NR	52.7/52.2	51.8/51.8	Phase III, double-blind, parallel-group, RCT, in 62 centres in USA, Mexico and India, DURATION-2 trial	2	Exenatide vs. pioglitazone	Metformin	100 mg/d	26
Nauck 2007 [660] NCT00082407	T2DM (*n*=501)	9.8±6.3/10.0±6.2	8.6±1.0/8.6±1.1	NR	58.8/58.5	46.6/50.8	Phase III, open-label, parallel-group RCT, in 69 centres in 12 countries	2	Exenatide vs. insulin aspart	Metformin ± sulfonylurea	5-10 µg/d	52
Inagaki 2012 [661] NCT00935532	T2DM (*n*=427)	8.9±6.1/9.2±5.9	8.5±0.8/8.5±0.8	NR	57.1/56.4	66.0/69.8	Phase III, open-label, parallel-group, RCT, in 22 centres in Japan	2	Exenatide vs. insulin glargine	Biguanide ± sulfonylurea ± TZDs	2 mg/week	26
Liraglutide therapy												
Marso 2016 [394] NCT01179048	T2DM with high risk CVD and/or CKD (*n*=9340)	12.7±8.0/8.7±1.5	12.9±8.1/8.7±1.5	Stroke/TIA 730 (15.6%) vs. 777 (16.6%)	64.2/64.4	64.5/64.0	Double-blind, parallel-group, RCT, in 410 centres in 32 countries, LEADER trial	2	Liraglutide vs. placebo	≤2 AHG agents + insulin	0.6-1.8 mg/d	198**
Seino 2016 [662] NCT01572740	T2DM (*n*=257)	14.3±8.9/14.7±8.6	8.8±0.9/8.8±0.9	NR	61.3/59.8	54.3/57.7	Phase III, double-blind, parallel-group, RCT, in 23 centres in Japan	2	Liraglutide vs. placebo	Insulin	0.3, 0.6, 0.9 mg/d	36
Kaku 2011 [663] NCT00393718	T2DM (*n*=400)	8.1±6.7/8.5±6.8	9.3±1.1/9.2±0.9	NR	58.2/58.5	68.3/65.2	Phase III, double-blind, parallel-group, RCT, in Japan	2	Liraglutide vs. glibenclamide	NR	0.9 mg/d	52
Bailey 2016 [664] NCT01907854	T2DM (*n*=406)	7.9±5.7/7.6±6.2	8.3±0.6/8.2±0.6	NR	56.3/56.5	57.9/61.3	Phase IV, double-blind, parallel-group, RCT, in 106 centres in 7 countries, LIRA-SWITCH trial	2	Liraglutide vs. sitagliptin	Metformin + sitagliptin	Liraglutide 0.6-1.8 mg/d Sitagliptin 100 mg/d	26
Lingvay 2016 [665] NCT01952145	T2DM (*n*=557)	11.6±7.4/11.3±6.6	8.4±0.9/8.2±0.9	NR	58.4/59.1	51.4/49.1	Phase III, double-blind, parallel-group, RCT, in 91 centres in 10 countries, DUAL-V trial	2	Liraglutide/insulin degludec vs. insulin glargine	Metformin	0.6 mg/d/16 units IDeg	27
NCT01117350 [666]	T2DM (*n*=1125)	8.4(4.8-11.7)/8.5(5.2-12.4)**	9.1±1.1/9.0±1.1	NR	57.4/57.1	55.9/52.7	Phase IV, open-label, parallel-group, RCT, in 136 centres in 17 countries, EAGLE trial	2	Liraglutide vs. insulin glargine	Metformin	0.6, 1.2, 1.8 mg/d	48
Lixisenatide therapy												
Pfeffer 2015 [395] NCT01147250	T2DM with recent ACS (*n*=6068)	9.2±8.2/9.4±8.3	7.7±1.3/7.6±1.3	Stroke 143 (4.7%) vs. 188 (6.2%)	59.9/60.6	69.6/69.1	Phase III, double -blind, parallel-group, RCT, 49 countries, ELIXA trial	2	Lixisenatide vs. placebo	AHG agents	10-20 mg/week	109
Semaglutide therapy												
Marso 2016 [401] NCT01720446	T2DM with established CVD and/or CKD (*n*=3297)	13.9±8.1/8.7±1.5	8.7±1.4/8.7±1.5	IS=178 (10.8%) vs. 205 (12.3%) HS=52 (4.9%) vs. 56 (3.4%)	64.7/64.6	61.5/60.0	Double-blind, parallel-group, RCT, in 230 centres in 20 countries, SUSTAIN-6 trial	4	Semaglutide vs. placebo	≤2 AHG agents	0.5-1 mg/week	104
Husain 2019 [396] NCT02692716	T2DM with established CVD and/or CKD (*n*=3183)	14.7±8.5/15.1±8.5	8.2±1.6/8.2±1.6	NR	66.0/66.0	61.5/60.0	Double-blind, parallel-group, RCT, in 214 centres in 21 countries, PIONEER-6 trial	4	Semaglutide vs. placebo	AHG agents	14 mg/d	69**
Taspoglutide therapy												
Raz 2012 [667] NCT00744926	T2DM (*n*=368)	2.5±2.7/2.3±1.9	7.6±1.0/7.6±1.0	NR	54.2/55.8	36.5/37.0	Phase III, double-blind, parallel-group, RCT, 53 countries, T-emerge 1 trial	3	Taspoglutide vs. placebo	None	10-20 mg/week	24
NCT01018173 [668]	T2DM with established CVD (*n*=2118)	NR	NR	NR	63.3/63.3	65.0/65.0	Double-blind, parallel-group RCT, in 288 centres in 25 countries, T-EMERGE-8 trial	2	Taspoglutide vs. placebo	NR	10-20 mg/week	104

Bergenstal 2012 [599] NCT00754988	T2DM (*n*=469)	5.9±4.8/5.5±3.9	7.9±0.9/8.0±0.8	NR	54.2/56.1	55.3/52.2	Phase III, double-blind, parallel-group RCT in 149 centres in 23 countries, T-Emerge 4 trials	2	Taspoglutide vs. placepo	Metformin	10-20 mg/week	156
Hollander 2012 [669] NCT00823992	T2DM obese (*n*=304)	5.2±4.3/4.9±4.1	7.5±40.8/7.6±0.8	NR	53.0/54.0	42.0/39.0	Phase III, double-blind 24 weeks, 28 week open-label extension phase, parallel-group RCT, in 63 centres in 8 countries, T-Emerge 7 trial	2	Taspoglutide vs. placebo	Metformin ± sulfonylurea	20 mg/week	52
Henry 2012 [670] NCT00744367	T2DM (*n*=324)	7.8±4.9/7.5±5.8	8.2±1.0/8.1±0.9	NR	54.0/54.3	56.0/50.0	Phase III, double-blind 24 weeks, 28 week open-label extension phase, parallel-group RCT in 113 centres in 8 countries T-Emerge 3 trial	3	Taspoglutide vs. placebo	Metformin + pioglitazone	10-20 mg/week	24
Pratley 2012 [671] NCT00909597	T2DM (*n*=751)	8.9±6.3/8.6±6.1	8.3±0.9/8.3±0.8	NR	56.4/57.1	47.5/51.0	Double-blind, parallel-group RCT in 130 centres in 17 countries, T-Emerge 6 trial	3	Taspoglutide vs. pioglitazone	Sulfonylurea ± metformin	10-20 mg/week	24
Rosenstock [672] 2013 NCT00717457	T2DM (*n*=1173)	6.6±5.5/6.5±5.4	8.1±0.9/8.1±0.9	NR	56.0/55.0	55.0/49.0	Phase III, open-label, parallel-group, RCT, in 189 centres in 23 countries, T-emerge 2 trial	3	Taspoglutide vs. exenatide	Metformin ± TZDs	10-20 md/week	104
Nauck 2013 [673] NCT00755287	T2DM (*n*=1037)	9.0±6.0/10.0±6.0	5.5±10.0/5.6±10.0	NR	58.0/NR	53.0/NR	Phase III, open-label 24 weeks, 28 weeks single blind extension phase, parallel-group RCT in 187 centres in 25 countries, T-Emerge 4 trials	3	Taspoglutide vs. insulin glargine	Metformin + sulfonylurea	10-20 mg/week	24

Abbreviations*: ACS*, acute coronary syndrome; *ACE*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptors blocker; *AHG*, anti-hyperglycaemic drugs; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease; C*RF*, chronic renal failure; *CHF*, congestive heart failure; *IGT*, impaired glucose tolerance; *IS*, ischaemic stroke; *HS*, haemorrhagic stroke; *mμ/d*, microgram pear day; *mg/d*, milligram pear day; *NR*, not report; *RCT*, randomised controlled trial; *TZDs*, thiazolidinedione; *T2DM*, type 2 diabetes mellitus.
Note: ‡ Mean age and dosages present for intervention drugs; ** Median age; ** Median year; ** Median (interquartile range); ¶ Novel treatment of fixed-dose combination of 2 different classes of AHG; †values are expressed as mean ± SD or ǂ mean ± SE.

3.5.3 SGLT2-Is therapies

Supplemental Table 3-6. Baseline characteristics of SGLT2-Is therapies included trials

Study Trial registry	Population Sample size	T2DM† Mean duration (years)	HbA1C levels %	Prior stroke / TIA (*n*, %)	Mean age (years)‡	Males (%)	Study design and country	Parallel arms	Intervention vs. comparator	Background AHGs therapy	SGLT2-Is dosage‡ mg/day	Duration (weeks)
Canagliflozin therapy												
Inagaki 2013 [674] NCT01022112	T2DM (*n*=382)	NR	8.1±0.8/7.9±0.8	NR	57.3/57.7	67.4/72.0	Phase II, double-blind, parallel-group RCT, in 6 centres in Japan	5	Canagliflozin vs. placebo	None	50, 100, 200, 300	12
Inagaki 2014 [675] NCT01413204	T2DM (*n*=272)	5.3±5.3/5.6±5.8	8.0±0.8/8.0±0.7	NR	57.9/58.2	73.8/64.5	Phase III, double-blind, parallel-group RCT, in 31 centres in Japan	3	Canagliflozin vs. placebo	None	100-200	24
Stenlöf 2012 [676] NCT01081834	T2DM (*n*=584)	4.4±4.5/4.2±4.1	8.0±1.0/8.0±1.0	NR	55.0/55.7	44.7/45.8	Phase III, double-blind, parallel-group RCT, in 79 centres in 18 countries	3	Canagliflozin vs. placebo	None	100-200	26
Weir 2014 [677] NCT01064414	T2DM with CKD (*n*=436)	NR	NR	NR	68.7/68.2	59.2/63.3	Phase III, double-blind, parallel-group RCT, in 109 centres in 18 countries	3	Canagliflozin vs. placebo	None	100-200	52
Sha 2014 [678] NCT01483781	T2DM (*n*=35)	8.6±4.0/8.4±4.6	7.6±0.5/7.7±0.6	NR	63.3/62.3	89.0/83.0	Phase I, double-blind, parallel-group RCT, in Germany	2	Canagliflozin vs. placebo	Metformin	300	12
Qiu 2014 [679] NCT01340664	T2DM (*n*=279)	7.05±.5/7.0±6.4	7.6±0.9/7.7±0.9	NR	57.7/57.0	45.2/49.5	Phase II, double-blind, parallel-group RCT, in 64 centres in 7 countries	3	Canagliflozin vs. placebo	Metformin	50-150	18
Rosenstock 2012 [601] NCT00642278	T2DM (*n*=386)	5.9±5.0/6.4±5.0	7.7±0.9/7.8±0.8	NR	53.1/52.5	51.0/53.1	Phase II, double-blind, parallel-group RCT, in 85 centres in 13 countries	6	Canagliflozin vs. placebo	Metformin	50, 100, 200, 300, 600	12
Ji 2015 [680] NCT01381900	T2DM (*n*=676)	6.8±4.7/6.4±4.6	8.0±0.9/7.9±0.9	NR	56.5/55.8	52.7/55.3	Phase III, double-blind, parallel-group RCT, in 25 centres in China, Malaysia and Vietnam	3	Canagliflozin vs. placebo	Metformin ± sulfonylurea	100-300	18
Wilding 2013 [681] NCT01106625	T2DM (*n*=469)	9.2±5.1/10.3±6.7	8.1±0.9/8.1±0.9	NR	56.7/56.7	52.1/48.7	Phase III, double-blind, parallel-group RCT, in 76 centres in 12 countries, CANTATA-MSU Trial	3	Canagliflozin vs. placebo	Metformin + sulfonylurea	100-300	52
Fulcher 2015 [682] NCT01032629	T2DM at risk of CVD (*n*=127)	9.5±6.1/11.4±6.7	8.2±0.9/8.5±1.1	NR	64.8/64.8	56.0/58.0	Double-blind, parallel-group, RCT, CANVAS trial	3	Canagliflozin vs. placebo	Sulfonylurea	100-300	72-84
Cai 2018 [683] NCT02025907	T2DM (*n*=216)	9.6±6.1/6.9±5.3	8.2±0.9/7.9±0.9	NR	57.4/57.5	61.7/51.9	Phase IV, double-blind, parallel-group, RCT, in 57 centres in 5 countries	2	Canagliflozin vs. placebo	Metformin + sitagliptin	100-300	28
Bode 2015 [525] NCT01106651	T2DM (*n*=312)	NR	NR	NR	63.9/63.2	53.1/60.3	Phase III, double-blind, parallel-group RCT, in 90 centres in 17 countries	3	Canagliflozin vs. placebo	± AHG agents	100-300	104
Lavalle-González 2013 [684] NCT01106677	T2DM (*n*=549)	6.9±5.4/6.8±5.3/6.9±5.4	7.9±0.9/8.0±0.9/7.9±0.9	NR	55.4/46.2	55.3/51.4	Phase III, double-blind, parallel-group, RCT, in 128 centres in 22 countries	4	Canagliflozin vs. placebo + sitagliptin	Metformin	Canagliflozin 100-300 Sitagliptin 100	24
Forst 2014 [513] NCT01106690	T2DM (*n*=342)	10.8±7.1/10.1±6.6	8.0±0.9/8.0±1.0	NR	56.9/58.3	61.7/66.1	Phase III, double-blind, parallel-group RCT, in 74 centres in 11 countries	3	Canagliflozin vs. placebo + sitagliptin	Metformin + pioglitazone	Canagliflozin 100-300 mg/d Sitagliptin 100	26
Rosenstock 2016 [685] NCT01809327	T2DM (*n*=1186)	4.1±4.0/3.3±4.5	8.8±1.2/8.8±1.2	NR	54.9/55.2	47.7/48.9	Phase III, double-blind, parallel-group, RCT, in 134 centres in 12 countries	5	Canagliflozin vs. metformin	None	100-300	12
Cefalu 2013 [686] NCT00968812	T2DM (*n*=1450)	6.6±5.5/6.6±5.0	7.8±0.8/7.8 ±0.8	NR	56.1/56.3	51.0/55.0	Phase III, double-blind, parallel-group RCT, in 157 centres in 19 countries, CANTATA-SU trial	3	Canagliflozin vs. glimepiride	Metformin	100-300	52
Schernthaner 2013 [687] NCT01137812	T2DM (*n*=755)	9.7±6.3/9.4±6.1	8.1±0.9/8.1±0.9	NR	56.5/56.6	55.0/56.9	Phase III, double-blind, parallel-group RCT, in 184 centres in 17 countries	2	Canagliflozin vs. sitagliptin	Metformin + sulfonylurea	Cangagliflozin 300 Sitagliptin 100	52

Dapagliflozin therapy												
Wiviott 2019 [397] NCT01730534	T2DM at risk of CVD (*n*=17160)	11.0(6.0-16.0)/10.0(6.0-16.0)**	8.3±1.2/8.3±1.2	CVD=653 (7.6) vs. 648 (7.6%)	63.9/64.0	63.1/62.1	Phase III, double-blind, parallel-group RCT, in 882 centres in 33 countries, DECLARE-TIMI58 trial	5	Dapagliflozin vs. placebo	None	10	219**
Kaku 2013 [688] NCT00972244	T2DM (*n*=279)	4.8±4.4/4.7±3.8	8.1±0.7/8.1±0.7	NR	57.0/58.4	76.3/79.6	Phase IIb, double-blind, parallel-group RCT, in 26 centres in Japan	5	Dapagliflozin vs. placebo	None	1, 2.5, 5, 10	12
Bailey 2012 [689] NCT00736879	T2DM (*n*=282)	1.5±2.7/1.1±1.9	7.9±1.0/7.8±1.1	NR	52.8/53.5	48.6/54.4	Phase III, double-blind, parallel-group RCT, in 63 centres in 7 countries	4	Dapagliflozin vs. placebo	None	1, 2.5, 5	24
Kaku 2014 [690] NCT01294423	T2DM (*n*=261)	4.5±5.0/5.3±6.2	7.5±0.7/7.5±0.6	NR	58.1/60.4	59.2/59.8	Phase III, double-blind, parallel-group RCT, in 27 centres in Japan	3	Dapagliflozin vs. placebo	None	5-10	24
Bailey 2014 [691] NCT00528372	T2DM (*n*=274)	1.8±2.8/2.1±3.1	7.9±0.9/7.8±0.8	NR	52.1/52.7	50.8/41.3	Phase III, double-blind, parallel-group RCT, in 85 centres in 4 countries	4	Dapagliflozin vs. placebo	None	2.5, 5, 10	102
Schumm-Draeger 2015 [692] NCT01217892	T2DM (*n*=400)	5.1±4.0/5.5±4.2	7.8±0.7/7.9±0.8	NR	57.4/58.5	44.4/46.5	Phase III, double-blind, parallel-group RCT, in 54 centres in 7 countries	4	Dapagliflozin vs. placebo	Metformin	5-10	16
Bailey 2010 [693] NCT00528879	T2DM (*n*=546)	6.2±5.8/5·85±·1	8.0±0.9/8·1±0·9	NR	54.0/53.7	52.8/55.5	Phase III, double-blind, parallel-group RCT, in 75 centres in 5 countries	4	Dapagliflozin vs. placebo	Metformin	2.5, 5, 10	104
Bolinder 2014 [694] NCT00855166	T2DM (*n*=182)	6.0±4.5/5.5±5.3	7.2±0.4/7.2±0.5	NR	60.6/60.8	55.1/56.0	Phase III, double-blind, parallel-group RCT, in 40 centres in 5 countries	2	Dapagliflozin vs. placebo	Metformin	10	102
Ji 2014 [695] NCT01095653	T2DM (*n*=393)	1.4±2.6/1.3±2.0	8.2±0.8/8.4±0.9	NR	53.0/51.2/49.9	65.6/64.6/65.9	Phase III, double-blind, parallel-group, RCT, in 39 centres in 4 countries	3	Dapagliflozin vs. placebo	Metformin	5-10	24
Henry 2012 [696] (Study 1) NCT00643851	T2DM (*n*=598)	1.6±2.8/1.6±2.6	9.2±1.3/9.2±1.3	NR	52.0/51.8	42.8/47.3	Phase III, double-blind, parallel-group RCT, in 105 centres in 4 countries	3	Dapagliflozin vs. placebo	Metformin	5	24
Henry 2012 (Study 2) [696] NCT00859898	T2DM (*n*=638)	2.2±3.6/1.9±4.0	9.1±1.3/9.1±1.3	NR	51.1/52.7	49.1/46.6	Phase III, double-blind, parallel-group RCT, in 131 centres in 4 countries	3	Dapagliflozin vs. placebo	Metformin	10	24
Heerspink 2013 [697] NCT00976495	T2DM (*n*=49)	6.5±4.4/6.5±5.0	7.7±0.6/7.5±1.0	NR	53.7/58.0	66.7/72.0	Phase II, double-blind, parallel-group RCT, in 12 centres in USA, Canada and Netherlands	2	Dapagliflozin vs. placebo	Metformin + sulfonylurea	10	12
Matthaei 2015 [698] NCT01392677	T2DM (*n*=218)	9.3±6.5/9.6±6.2	8.1±0.9/8.2±0.9	NR	61.1/60.9	42.6/55.6	Phase III, double-blind, parallel-group RCT, in 47 centres in 6 countries	2	Dapagliflozin vs. placebo	Metformin + sulfonylurea	10	52
Mathieu 2015 [607] NCT01646320	T2DM (*n*= 320)	7.2±5.7/8.0±6.6	8.2±0.9/8.2±0.9	NR	55.2/55.0	43.8/47.5	Phase III, double-blind, parallel-group RCT, in 67 centres in 8 countries	2	Dapagliflozin vs. placebo	Metformin + sitagliptin	10	24
Jabbour 2014 [699] NCT00984867	T2DM (*n*=451)	5.7±4.9/5.6±5.4	7.9±0.8/8.0±0.8	NR	54.8/55.0	57.0/52.7	Phase III, double-blind, parallel-group RCT, in 88 centres in 6 countries	2	Dapagliflozin vs. placebo	± Metformin + sitagliptin	10	24
Wilding 2012 [700] NCT00357370	T2DM (*n*=71)	13.6±7.2/13.5±7.3	8.5±0.8/8.5±0.8	NR	56.0/58.4	50.0/69.6	Phase II/III, double-blind, parallel-group, un-controlled RCT, in 23 centres in USA and Canada	4	Dapagliflozin vs. placebo	Metformin ± TZDs + insulin	10-20	12
Mudaliar 2014 [701]	T2DM (*n*=44)	9.9±6.5/6.4±5.0	7.5±0.8/7.5±0.7	NR	56.2/53.3	65.2/66.7	Phase IIb, double-blind, parallel-group RCT	2	Dapagliflozin vs. placebo	Metformin ± insulin secretagogue	5	12
NCT00831779 [702]	T2DM (*n*=44)	NR	NR	NR	56.2/53.3	65.2/66.7	Phase II, double-blind, parallel-group, RCT, in 3 centres in USA	2	Dapagliflozin vs. placebo	Metformin ± insulin	5	24
Strojek 2011 [703] NCT00680745	T2DM (*n*=596)	7.4±5.7/7.4±5.7	8.1±0.8/8.2±0.7	NR	59.7/60.3	48.0/49.0	Phase III, double-blind, parallel-group RCT, in 66 centres in 7 countries	4	Dapagliflozin vs. placebo	Sulfonylurea	2.5, 5, 10	24
Kohan 2014 [704] NCT00663260	T2DM with CKD (*n*=252)	17.6±9.5/15.7±9.5	8.3±1.0/8.5±1.3	NR	67.0/67.0	66.1/63.1	Phase II/III, double-blind, parallel-group RCT, in 96 centres in 13 countries	3	Dapagliflozin vs. placebo	Sulfonylurea ± TZDs ± insulin	5-10	104
Rosenstock 2012 [526] NCT00683878	T2DM (*n*=420)	5.7±5.9/5.1±5.0	8.4±0.9/8.3±1.0	NR	53.5/53.5	48.7/51.1	Phase III, double-blind, parallel-group RCT, in 89 centres in 9 countries	3	Dapagliflozin vs. placebo	Pioglitazone	5-10	48
Weber 2016 [705] NCT01195662	T2DM (*n*=582)	7·7±5·9/7·3±5·0	8·1±0·9/8·0±1·0	NR	56.0/57.0	52.4/57.6	Phase III, double-blind, parallel-group RCT, in 298 centres in 16 countries	2	Dapagliflozin vs. placebo	TZDs ± insulin	10	12
NCT01137474 [706]	T2DM CKD on ACE ± ARB (*n*=944)	NR	NR	NR	NR	55.8/55.0	Phase III, double-blind, parallel-group RCT, in 329 centres in 16 countries	4	Dapagliflozin vs. placebo	TZDs ± insulin	2.5, 5, 10	12
Wilding 2014 [707] NCT00673231	T2DM (*n*=807)	13.6±7.2/13.5±7.3	8.6±0.8/8.5±0.8	NR	59.5/58.8	45.5/49.2	Phase III, double-blind, parallel-group RCT, in 96 centres in 13 countries	4	Dapagliflozin vs. placebo	Insulin	2.5, 5, 10	104

Yang 2018 [708] NCT02096705	T2DM (*n*=272)	12.7±7.2/12.2±6.7	8.5±0.7/8.5±0.8	NR	56.5/58.6	47.5/48.1	Phase III, double-blind, parallel-group, RCT, in 29 centres in 7 countries	2	Dapagliflozin vs. placebo	Insulin	10	24
Cefalu 2015 [709] NCT01031680	T2DM with CVD and hypertension (*n*=922)	12.6±8.7/12.3±8.2	8.2±0.8/8.1±0.8	Stroke/TIA 100 (22%) vs. 89 (19.4%)	62.8/63.0	67.9/68.6	Phase III, double-blind, parallel-group RCT, in 141 centres in 5 countries	2	Dapagliflozin vs. placebo	AHG agents	10	104
Leiter 2014 [710] NCT01042977	T2DM with CVD (*n*=965)	13.5±8.2/13.0±8.4	8.0±0.8/8.1±0.8	Stroke/TIA 105 (21.9%) vs. 84 (17.4%)	63.9/63.6	66.8/67.0	Phase III, double-blind, parallel-group RCT, in 173 centres in 6 countries	2	Dapagliflozin vs. placebo	AHG agents	10	52
List 2009 [711] NCT00263276	T2DM (*n*=359)	NR	7.8±0.9/7.8±0.9	NR	55.0/53.5	49.8/52.0	Phase II, double-blind, parallel-group RCT, in 145 centres in USA, Canada, Mexico and Puerto Rico	7	Dapagliflozin vs. placebo + metformin	None	2.5, 5, 10, 20, 50	12
Nauck 2014 [712] NCT00660907	T2DM (*n*=814)	6.0±5.0/7.0±6.0	7.7±0.9/7.7±0.9	NR	58.1/58.6	55.3/54.9	Phase III, double-blind, parallel-group RCT, in 95 centres in 10 countries	2	Dapagliflozin vs. glipizide	Metformin	10	156
Rosenstock 2015 [713] NCT01606007	T2DM (*n*=534)	7.1±5.0/7.4±5.4/8.2±5.5	8.9±1.2/8.9±1.2/9.0±1.1	NR	53.5/54.0	49.7/50.5	Phase III, double-blind, parallel-group RCT, in 139 centres in 8 countries	3	Dapagliflozin vs. saxagliptin	Metformin	Dapagliflozin 10 Saxagliptin 5	24
Empagliflozin therapy												
Kadowaki 2015 [714] NCT01193218	T2DM (*n*=861)	NR	7.9±0.7/NR	NR	57.3/58.7	75.4/73.4	Phase II, double-blind, parallel-group RCT, in 32 centres in Japan	5	Empagliflozin vs. placebo	None	5, 10, 25, 50	12
NCT01649297 [715]	T2DM (*n*=983)	NR	NR	NR	58.3/57.9	54.2/55.0	Phase II, double-blind, parallel-group RCT, in 139 centres in 18 countries	5	Empagliflozin vs. placebo	Metformin	5, 10, 12.5, 25	16
Merker 2015 [716] NCT01289990; NCT01159600	T2DM (*n*=637)	≤1->10/≤1->10	8.1±0.8/8.2±0.8	NR	54.7/56.4	54.9/52.8	Phase III, double-blind, open-label extension period, parallel-group, RCT, in 148 centres in 12 countries, EMPA-REG EXTEND™ MET trial	3	Empagliflozin vs. placebo	Metformin	10-25	76
Ha¨ring 2013 [717] NCT01159600	T2DM (*n*=500)	≤1->10/≤1->10	9.1±0.9/8.2±0.8	NR	54.8/56.5	55.0/53.0	Phase III, double-blind, empagliflozin open-label, parallel-group RCT, in 148 centres in 12 countries	4	Empagliflozin vs. placebo	Metformin ± sulfonylurea	10-25	24
Rosenstock 2015 [718] NCT01011868	T2DM (*n*=494)	≤1->5/≤1->5	8.3±0.8/8.2±0.8	NR	59.3/58.1	54.5/53.0	Phase IIb, double-blind, parallel-group, RCT, in 99 centres in 7 countries	3	Empagliflozin vs. placebo	± Metformin ± sulfonylurea ± insulin	10-25	78
Zinman 2015 [398] NCT01131676	T2DM with established CVD and CKD (*n*=7020)	≤1->10/≤1->10	8.1±0.9/8.1±0.8	Stroke 1084 (23.1%) vs. 553 (23.7%)	63.0/63.2	71.2/72.0	Double-blind, parallel-group, RCT in at 590 sites in 42 countries, EMPA-REG OUTCOME trial	3	Empagliflozin vs. placebo	Metformin ± sulfonylurea ± insulin	10-25	161**
Barnett 2014 [676] NCT01164501	T2DM with CKD (*n*=738)	≤1->10/≤1->10	7.9±0.8/8.1±0.8	NR	63.6/64.1	60.1/56.7	Phase III, double-blind, parallel-group RCT, in 127 centres in 15 countries	3	Empagliflozin vs. placebo	Metformin ± sulfonylurea ± insulin	10-25	24
Rosenstock 2014 [719] NCT01306214	T2DM (*n*=563)	≤1->10/≤1->10	8.3±0.7/8.3±0.7	NR	57.4/55.3	39.9/48.3	Phase III, double-blind, parallel-group RCT, in 103 centres in 14 countries	3	Empagliflozin vs. placebo	Metformin ± insulin	10-25	52
Kovacs 2014 [514] NCT01210001	T2DM (*n*=498)	>10.0/>10.0	8.1±0.8/8.2±0.9	NR	54.5/54.6	50.4/44.2	Phase III, double-blind, parallel-group, RCT, in 68 centres in 7 countries	3	Empagliflozin vs. placebo	± Metformin + pioglitazone	10-25	24
Kovacs 2014 [514] NCT01289990	T2DM (*n*=498)	≤1->10/≤1->10	8.1±0.8/8.2±0.9	NR	54.0/55.6	55.6/51.0	Phase III, double-blind, parallel-group, RCT, in 69 centres in 8 countries, EMPA-REG PIO™ trial	3	Empagliflozin vs. placebo	Pioglitazone	10-25	76
Tikkanen 2015 [720] NCT01370005	T2DM with hypertension (*n*=824)	≤1->10/≤1->10	7.8±0.7/7.9±0.7	NR	60.3/60.3	59.2/62.0	Phase III, double-blind, parallel-group RCT, in 120 centres in 12 countries, EMPA-REG BP trial	3	Empagliflozin vs. placebo	AHG agents	10-25	12
Roden 2013 [593] NCT01177813	T2DM (*n*=763)	≤1->10≤1->10	9.1±1.0/7·9±0·8	NR	53.4/55.0	67.2/58.6	Phase III, double-blind, parallel-group RCT, in 124 centres in 9 countries	4	Empagliflozin vs. placebo	None	10-25	24
Søfteland 2017 [550] NCT01734785	T2DM (*n*=332)	≤1->10/≤1->10	7.9±0.8/7.9±0.8	NR	54.9/55.9	61.7/55.5	Phase III, double-blind, parallel-group, RCT, in 90 centres in 11 countries	3	Empagliflozin vs. placebo	Metformin	10-25	24
Rosenstock 2013 [602] NCT00749190	T2DM (*n*=162)	NR	7.9±0.7/8.1±0.9	NR	58.1/58.7	50.7/50.0	Phase II, double-blind, parallel-group RCT, in 116 centres in 16 countries	6	Empagliflozin vs. placebo	Metformin	1, 5, 10, 25, 50	12
Ferrannini 2013 [721] NCT00789035	T2DM (*n*=406)	NR	7.9±0.8/7.9±0.9	NR	57.7/57.3	52.1/51.9	Phase IIb, double-blind, parallel-group RCT, open-label metformin, in 74 centres in 13 countries	5	Empagliflozin vs. placebo + metformin	None ± AHGs agents	5, 10, 25	12
Ferrannini 2013 (Study 1) [721] NCT00881530	T2DM (*n*=271)	≤1->5/≤1->5	7.9±0.8/8.2±0.9	NR	58.8/56.8	48.9/50.0	Phase IIb, open-label, parallel-group RCT, in 132 centres in 21 countries	3	Empagliflozin vs. metformin	None	5, 10, 25	78

Hadjadj 2016 [722] NCT01719003	T2DM (*n*=1373)	≤1->10/≤1->10	7.1±1.2/7.0±1.2	NR	52.6/52.5	57.3/53.7	Phase III, double-blind, parallel-group, RCT, in 190 centres in 21 countries	9	Empagliflozin vs. metformin	None	10-25	26
Araki 2015 [503] NCT01368081	T2DM (*n*=1160)	≤1->10/≤1->10	7.8±0.8/7.9±0.8	NR	61.0/60.0	70.6/74.6	Phase III, double-blind, parallel-group, RCT, in 86 centres in Japan	13	Empagliflozin vs. metformin	Sulfonylurea ± glinide ± biguanide ± TZDs ± α-glucosidase-Is ± DPP-IV	10-25	52
Ridderstra°le 2014 [723] NCT01167881	T2DM (*n*=1545)	≤1->10/≤1->10	7·9±0·8/7·9±0·9	NR	56.2/55.7	56.5/54.0	Phase III, double-blind, parallel-group, RCT, in 182 centres in 23 countries	2	Empagliflozin vs. glimepiride	Metformin	25	104
DeFronzo 2015 [724] NCT01422876	T2DM (*n*=674)	≤1->10/≤1->10	8.0±0.8/8.0±0.9	NR	56.2/56.2	54.6/50.0	Phase III, double-blind, parallel-group RCT, in 197 centres in 22 countries	5	Empagliflozin vs. linagliptin	Metformin	10-25	52
Ferrannini 2013 (Study 2) [721] NCT00881530	T2DM (*n*=271)	≤1->5/≤1->5	7.8±0.8/8.0±0.9	NR	58.8/58.6	48.9/51.9	Phase IIb, double-blind empagliflozin, open-label sitagliptin, parallel-group RCT, in 132 centres in 21 countries	3	Empagliflozin vs. sitagliptin	Metformin	Empagliflozin 10-25 Sitagliptin 100	78
Ertugliflozin therapy												
Dagogo-Jack 2018 [725] NCT02036515	T2DM with atherosclerosis (*n*=462)	9.5±5.7/9.4±5.6	8.1±0.9/8.0±0.9	NR	59.5/58.3	52.8/65.4	Phase III, double-blind, RCT, in 149 centres in 23 countries, VERTIS CV trial	3	Ertugliflozin vs. placebo	Metformin + sitagliptin	5-15	318
Miller 2018 [726] NCT02226003	T2DM (*n*=291)	6.1±5.7/6.8±6.5	8.9±0.9/9.0±0.9	NR	56.3/54.3	56.7/58.8	Phase III, double-blind, parallel-group, RCT	3	Ertugliflozin + sitagliptin[¶] vs. placebo	None or metformin, α-glucosidase-Is, sulfonylureas and glinides	Ertugliflozin 5-15 Sitagliptin 100	26
Amin 2015 [609] NCT01059825	T2DM with hypertension (*n*=648)	6.3±0.8/6.4±0.9	8.2±0.1/8.2±0.1	NR	53.6/55.1	48.2/63.2	Phase II, double-blind, parallel-group, RCT	6	Ertugliflozin vs. placebo + metformin	AHG agents	1, 5, 10, 25	12
Ipragliflozin therapy												
Wilding 2013 [727] NCT01117584	T2DM (*n*=342)	6.0±5.3/5.7±3.2	7.8±0.7/7.7±0.6	NR	57.4/75.3	50.4/54.5	Phase II, double-blind, parallel-group, RCT, in 45 centres in 6 countries	5	Ipragliflozin vs. placebo	Metformin	12.5, 50, 150, 300	12
Kashiwagi 2015 [728] NCT01135433	T2DM (*n*=168)	8.1±8.1/8.1±1.9	8.3±0.7/8.4±0.7	NR	56.2/57.7	58.9/58.9	Phase III, double-blind, parallel-group, RCT, in 7 centres in Japan, ILLUMINATE trial	2	Ipragliflozin vs. placebo	Metformin	50	24
Lu 2016 [729] NCT01505426	T2DM (*n*=170)	NR	NR	NR	NR	NR	Phase III, double-blind, parallel-group, RCT, in 12 centres in Korea and Taiwan	2	Ipragliflozin vs. placebo	Metformin	NR	24

Abbreviations: *ACS*, acute coronary syndrome; *ACE*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptors blocker; *AHG*, anti-hyperglycaemic drugs; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease; C*RF*, chronic renal failure; *CHF*, congestive heart failure; *IGT*, impaired glucose tolerance; *mμ/d*, microgram pear day; *mg/d*, milligram pear day; NR, not report; *RCT*, randomised controlled trial; *TZDs*, thiazolidinedione; *T2DM*, type 2 diabetes mellitus.
Note: [‡] Mean age and dosages present for intervention drugs; [**] Median age; [**]Median year; [**]Median (interquartile range); [¶]Novel treatment of fixed-dose combination of 2 different classes of AHG; †values are expressed as mean ± SD or [ǂ]mean ± SE.

3.6 Stroke results outcomes

3.6.1 DPP4-Is therapies

Supplemental Table 3-7. Studies results of stroke outcomes with DPP4-Is therapies

Study Trial registry	Type of stroke index event	Intervention of interest		Number of strokes				Ischaemic stroke				Haemorrhagic stroke				Fatal stroke			
		DPP4-Is (mg/day)	Controls (mg/day)	DPP4-Is		Controls		DPP4-Is		Controls		DPP4-Is		Controls		DPP4-Is		Controls	
				Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size
Alogliptin therapy																			
DeFronzo 2008 [530] NCT00286455	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	0	264	0	64	0 0	133 131	0	64			NR				NR	
Nauck 2009 [531] NCT00286442	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	0	423	0	104	0 0	213 210	0	104			NR				NR	
Pan 2017 [532] NCT01289119	SAEs	Alogliptin 25 Alogliptin 25 + metformin 1000 Alogliptin 25 + pioglitazone	Placebo Metformin Pioglitazone	1	252	0	253	0 0 1	92 99 61	0 0 0	92 98 63			NR				NR	
Pratley 2009 [533] NCT00286494	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	0	337	0	97	0 0	138 199	0	97			NR				NR	
White 2013 [386] NCT00968708	Non-fatal 1[ry] and 2[ry] outcome	Alogliptin	Placebo	29	2701	32	2679	29	2701	32	2679			NR				NR	
Rosenstock 2009 [534] NCT00286429	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	0	260	1	129	0 0	131 129	1	129			NR				NR	
Seino 2012 [535] NCT01318083; NCT01318135	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	1	209	0	103	1 0	105 104	0	103			NR				NR	
Pratley 2009 [536] NCT00286468	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	0	401	0	99	0 0	203 198	0	99			NR				NR	
Seino 2011 [537] NCT01263483	SAEs	Alogliptin 12.5 Alogliptin 25	Placebo	1	155	1	75	0 1	76	1	75			NR				NR	
DeFronzo 2012 [496] NCT00328627	SAEs	Alogliptin 12.5 + pioglitazone 15 Alogliptin 25 + pioglitazone 15 Alogliptin 12.5 + pioglitazone 30 Alogliptin 25+ pioglitazone 30 Alogliptin 12.5 + pioglitazone 45 Alogliptin 25 + pioglitazone 45	Placebo Placebo Placebo Placebo Placebo Placebo	2	1037	1	516	0 0 0 1 0 1	130 130 130 130 130 130	0 0 0 0 0 1	128 129 129 129 129 129			NR				NR	
Seino 2011 [538] NCT01263470	SAEs	Alogliptin 6.25 Alogliptin 12.5 Alogliptin 25 Alogliptin 50	Placebo Voglibose 0.6	1	322	0	158	1 0 0 0	79 84 80 79	0 0	75 83			NR				NR	
NCT01263496 [539]	SAEs	Alogliptin 6.25 Alogliptin 12.5 Alogliptin 25 Alogliptin 50	Voglibose 0.2	3	391	0	83	1 0 1 1	96 101 97 97	83	83			NR				NR	
Pratley 2014 [540] NCT01023581	SAEs	Alogliptin 12.5 Alogliptin 25 Alogliptin + metformin[¶] 12.5/500 Alogliptin + metformin[¶] 12.5/1000	Placebo Metformin 500 Metformin 1000	2	442	0	326	2 0 0 0	110 112 106 114	0 0 0	106 109 111			NR				NR	
Bosi 2011 [506] NCT00432276	SAEs	Alogliptin 25 + metformin 1500 + pioglitazone 30	Metformin 1500 + pioglitazone 4	1	404	1	399	1	404	1	399			NR				NR	
NCT00707993 [541]	SAEs	Alogliptin 25	Glipizide 5	1	222	1	219	1	222	1	219			NR				NR	

Del Prato 2014 [542] NCT00856284	SAEs	Alogliptin 12.5 + metformin Alogliptin 25 + metformin	Metformin + Glipizide	10	1751	3	869	4 5	873 878	3	869	1 0	873 878	0	869			NR					
Rosenstock 2010 [497] NCT00395512	SAEs	Alogliptin 25 Alogliptin 12.5 + pioglitazone 30 Alogliptin 25+ pioglitazone 30	Pioglitazone 30	0	491	1	163	0 0 0	164 163 164	1	163			NR				NR					
NCT01318070 [543]	SAEs	Alogliptin 12.5 Alogliptin 25	Pioglitazone	0	224	1	115	0 0	111 113	1	115			NR				NR					
Mita 2016 [544] UMIN000005311	AEs and SAEs	Alogliptin 25	Conventional treatment	0	161	2	161	0	161	2	161			NR				NR					
Dutogliptin therapy																							
Pattzi 2010 [545]	SAEs	Dutogliptin 200 Dutogliptin 400	Placebo	0	336	1	86	0 0	174 162	1	86			NR				NR					
Garcia-Soria 2008 [546]	SAEs	Dutogliptin 100 Dutogliptin 200 Dutogliptin 400	Placebo	0	133	1	41	0 0 0	43 44 46	1	41			NR				NR					
Linagliptin therapy																							
Rosenstock 2019 [387] NCT01897532	Fatal and non-fatal 1[ry] and 2[ry] outcome	Linagliptin 5	Placebo	81	3494	88	3485	65	3494	73	3485			NR			17	3494	16	3485			
Del Prato 2010 [547] NCT00621140	SAEs	Linagliptin 5	Placebo	0	336	0	167	0	336	0	167			NR				NR					
Taskinen 2011 [548] NCT00601250	SAEs	Linagliptin 5	Placebo	0	523	1	177	0	523	1	177			NR				NR					
Haak 2012 [549] NCT00798161	SAEs	Linagliptin 5 Linagliptin 2.5 + metformin 1000 Linagliptin 2.5 + metformin 2000 Linagliptin 2.5 + metformin 2000 (open-label)	Metformin 1000 Metformin 2000 Placebo	0	394	0	363	0 0 0 0	42 143 143 66	0 0 0	144 147 72			NR				NR					
Søfteland 2017 [550] NCT01734785	SAEs	Linagliptin 5	Placebo	0	606	0	110	0	606	0	110			NR				NR					
Owens 2011 [551] NCT00602472	SAEs	Linagliptin 5	Placebo	0	792	0	263	0	792	0	263			NR				NR					
Bajaj 2014 [552] NCT00996658	SAEs	Linagliptin 5	Placebo	0	183	0	89	0	183	0	89			NR				NR					
Barnett 2013 [553] NCT01084005	SAEs	Linagliptin 5	Placebo	1	162	0	79	1	162	0	79			NR				NR					
Lewin 2012 [554] NCT00819091	SAEs	Linagliptin 5	Placebo	0	161	0	84	0	161	0	84			NR				NR					
Gomis 2011 [555] NCT00641043	SAEs	Linagliptin 5	Placebo	0	259	0	130	0	259	0	130			NR				NR					
Yki-Järvinen 2013 [556] Duran-Garcia 2015 NCT00954447	SAEs	Linagliptin 5	Placebo	5	631	4	630	4	631	3	630	1	631	1	630			NR					
Wang 2016 [557] NCT01215097	SAEs	Linagliptin 5	Placebo	0	205	1	100	0	205	1	100			NR				NR					
1218.43[a] 2014 [558] NCT00800683	SEs	Linagliptin 5	Placebo	1	68	3	65	1	68	3	65			NR				NR					
McGill 2013 [559] PMCID: PMC3554278	AEs	Linagliptin 5	Placebo	1	68	1	65	1	68	1	65			NR				NR					
Groop 2017 [560] NCT01792518	SAEs	Linagliptin 5	Placebo	1	182	1	178	0	182	1	178	1	182	0	170			NR					
Kawamori 2012 [561] NCT00654381	SAEs	Linagliptin 5 Linagliptin 10	Placebo Voglibose 0.6	4	319	2	242	2 1	159 160	0 2	80 162	1 0	159 160	0 0	80 162			NR					
Mu 2017 [562] NCT01708902	SAEs	Linagliptin 5 Linagliptin 5 / linagliptin 2.5 Linagliptin 2.5 + metformin 1000 Linagliptin 2.5 + metformin 2000	Metformin 1000 Metformin 2000	1	713	1	289	1 0 0 0	251 31 212 219	1 0	145 144			NR				NR					
Haak 2013 [563] NCT00915772	SAEs	Linagliptin 2.5 + metformin 500 Linagliptin 2.5 + metformin 100	Metformin 1000	1	396	1	170	1 0	225 171	1	170			NR				NR					

NCT01204294; 2014 [499]		Linagliptin 5 + biguanide Linagliptin 5 + glinide Linagliptin 5 + Sulfonylure Linagliptin 5 + glitazone Linagliptin 5 + α-glucosidase-Is	Sulfonylure + metformin α-glucosidase -Is + metformin	2	450	1	124	1 0 0 0 0	82 66 143 74 85	1 0	63 61	0 0 1 0 1	82 66 143 74 85	0 0	63 61			NR			
Barnett 2012 [564] NCT00740051	SAEs	Linagliptin 5	Placebo + glimepiride 1-4	0	151	1	76	0	151	1	76			NR				NR			
Laakso 2015 [565] NCT01087502	SAEs	Linagliptin 5	Placebo + glimepiride 1-4	1	113	2	122	1	113	2	122			NR				NR			
Gallwitz 2012 [399] NCT00622284	Non-fatal SAEs	Linagliptin 5	Glimepiride	3	776	11	775	3	776	11	775			NR				NR			
Rosenstock 2019 [388] NCT01243424	Non-fatal SAEs	Linagliptin 5	Glimepiride	104	3023	120	3010	91	3023	104	3010			NR			13	3023	16	3010	
Omarigliptin therapy																					
Gantz 2017 [389] NCT01703208	Fatal and non-fatal stroke	Omarigliptin 25	Placebo	32	2092	34	2100	32	2092	34	2100			NR				NR			
Goldenberg 2017 [566] NCT01841697	SAEs	Omarigliptin 25	Sitagliptin 100	0	322	2	320	0	322	2	320			NR				NR			
Saxagliptin therapy																					
Pan 2012 [567] NCT00698932	SAEs	Saxagliptin 5	Placebo	1	284	0	284	1	284	0	284			NR				NR			
Rosenstock 2008 [568] NCT00950599	SAEs	Saxagliptin 2.5 Saxagliptin 5 Saxagliptin 10 Saxagliptin 20 Saxagliptin 40 Saxagliptin 100	Placebo	0	315	0	108	0 0 0 0 0 0	55 47 63 54 52 44	0	108			NR				NR			
Kumar 2014 [569] NCT00918879	SAEs	Saxagliptin 5	Placebo	0	107	0	106	0	107	0	106			NR				NR			
Frederich 2012 [570] NCT00316082	SAEs	Saxagliptin 2.5 (A.M.) Saxagliptin 2.5/5 (A.M.) Saxagliptin 5 (A.M.) Saxagliptin 5 (P.M)	Placebo	0	291	1	74	0 0 0 0	74 74 71 72	1	74			NR				NR			
Rosenstock 2013 [571] NCT00121641	SAEs	Saxagliptin 2.5 Saxagliptin 5 Saxagliptin 10 Saxagliptin 10 (open-label)	Placebo	2	372	0	95	0 1 0 0	102 106 98 66	0	95			NR				NR			
DeFronzo 2013 [571] NCT00121667	SAEs	Saxagliptin 2.5 + metformin Saxagliptin 5 + metformin Saxagliptin 10 + metformin	Placebo + metformin	5	564	0	179	1 1 3	192 191 181	0	179			NR				NR			
Yang 2011 [572] NCT00661362	SAEs	Saxagliptin 5 + metformin	Placebo + metformin	1	283	1	287	1	283	1	287			NR				NR			
Stenlöf 2010 [573] NCT00683657	SAEs	Saxagliptin 5 + metformin	Placebo + metformin	0	46	0	47	0	46	0	47			NR				NR			
White 2014 [574] NCT00885378	SAEs	Saxagliptin 5 + metformin	Placebo + metformin	0	74	0	86	0	74	0	86			NR				NR			
Chacra 2011 [575] NCT00313313	SAEs	Saxagliptin 2.5 + glyburide 7.5 Saxagliptin 5 + glyburide 7.5	Placebo + glyburide 7.5	1	501	2	267	1 0	248 253	1	267	0 0	248 253	1	267			NR			
Nowicki 2011 [576] NCT00614939	SAEs	Saxagliptin 2.5	Placebo	1	85	1	85	1	85	1	85			NR				NR			
Hollander 2011 [518] NCT00295633	SAEs	Saxagliptin 2.5 Saxagliptin 5	Placebo	4	381	1	184	3 0	195 186	1	184	0 1	195 186	0	184			NR			
Barnett 2012 [577] NCT00757588	SAEs	Saxagliptin 5	Placebo	0	304	2	151	0	304	2	151			NR				NR			
Scirica 2013 [390] NCT01107886	Fatal and non-fatal 1[ry] and 2[ry] outcome	Saxagliptin	Placebo	179	8280	176	8212	157	8280	141	8212			NR			22	8280	35	8212	
Henry 2011 [578] NCT00374907	SAEs	Saxagliptin 5	Placebo + metformin	0	20	0	16	0	20	0	16			NR				NR			
Jadzinsky 2009	SAEs	Saxagliptin 10 Saxagliptin 5 + metformin	Metformin	4	978	1	328	2 1	335 320	1	328	0 0	335 320	0	328			NR			

Pfützner 2011 [579] NCT00327015		Saxagliptin 10 + metformin						0	323			1	323										
Hermans 2012 [580] NCT01006590	SAEs	Saxagliptin 5	Metformin 1500	0	147	0	139	0	147	0	139			NR						NR			
Neutel 2013 [581] NCT00918138	SAEs	Saxagliptin 5	Metformin 1500	0	46	0	47	0	46	0	47			NR						NR			
Fonseca 2012 [582] NCT00960076	SAEs	Saxagliptin 5	Metformin 1500	0	138	0	144	0	138	0	144			NR						NR			
Göke 2013 [583] NCT00575588	SAEs	Saxagliptin 5 + metformin	Glipizide 15 + metformin	4	428	4	430	4	428	4	430			NR				1	428		0	430	
Schernthaner 2015 [584] NCT01006603	SAEs	Saxagliptin 5	Glimepiride ≤6	0	359	2	359	0	359	2	359			NR						NR			
Scheen 2010 [585] NCT00666458	SAEs	Saxagliptin 5 + metformin	Sitagliptin 100 + metformin	0	403	1	398	0	403	1	398			NR						NR			
Sitagliptin therapy																							
Hage 2014 [586] NCT00627744	AEs	Sitagliptin 100	Placebo	1	34	0	37	1	34	0	37			NR						NR			
Mohan 2009 [587] NCT00289848	SAEs	Sitagliptin 100	Placebo	1	352	0	178	1	352	0	178			NR						NR			
Barzilai 2011 [588] NCT00305604	SAEs	Sitagliptin 50-100	Placebo	0	102	0	104	0	102	0	104			NR						NR			
Ji 2016 [589] NCT01076088	SAEs	Sitagliptin 100 Sitagliptin 100 + metformin 1000 Sitagliptin 100 + metformin 1700	Metformin 100 Metformin 1700 Placebo	1	367	1	377	1 0 0	120 122 125	0 0 0	126 124 127	0 0 0	120 122 125	0 1 0	126 124 127					NR			
Scott 2007 [590] NCT00482079	SAEs	Sitagliptin	Placebo	0	495	0	125	0	495	0	125			NR						NR			
HU 2015 [591] NCT01289990	SAEs	Sitagliptin 100	Placebo	2	223	1	223	2	223	1	223			NR						NR			
Aschner 2006 [592] NCT00087516	SAEs	Sitagliptin 100 Sitagliptin 200	Placebo	1	488	1	253	0 1	238 250	1	253			NR						NR			
Roden 2013 [593] NCT01177813	SAEs	Sitagliptin 100	Placebo	2	223	1	229	2	223	1	229			NR						NR			
Hanefeld 2007 [594] NCT00481663	SAEs	Sitagliptin	Placebo	0	441	0	111							NR						NR			
Wang 2017 [595] NCT01177384	SAEs	Sitagliptin 100	Placebo	2	191	0	189	2	191	0	189			NR						NR			
Yang 2012 [596] NCT00813995	SAEs	Sitagliptin 100 + metformin 1500-1700	Placebo + metformin 1500-1700	2	197	1	198	2	197	1	198			NR						NR			
Raz 2008 [597] NCT00337610	SAEs	Sitagliptin 100	Placebo	0	96	0	94	0	96	0	94			NR						NR			
NCT00420511 [598]	SAEs	Sitagliptin 100	Placebo	0	10	0	11	0	10	0	11			NR						NR			
Bergenstal 2012 [599] NCT00754988	SAEs	Sitagliptin 100	Placebo	0	184	0	90	0	184	0	90			NR									
Gadde 2017 [600] NCT01652729	SAEs	Sitagliptin 100	Placebo	0	122	0	61	0	122	0	61			NR						NR			
Rosenstock 2012 [601] NCT00642278	SAEs	Sitagliptin 100	Placebo	0	65	0	65	0	65	0	65			NR						NR			
Rosenstock 2013 [602] NCT00749190	SAEs	Sitagliptin 100	Placebo	0	25	0	26	0	25	0	26			NR						NR			
Ba 2017 [603] NCT01590771	SAEs	Sitagliptin 100	Placebo	0	248	2	249	0	248	1	249	0	248	1	249					NR			
Dobs 2013 [604] NCT00350779	SAEs	Sitagliptin 100	Placebo	1	170	2	341	1	170	0	341	0	170	2	341					NR			
Fonsec 2013 [511] NCT00885352	SAEs	Sitagliptin 100	Placebo	0	157	0	156	0	157	0	156			NR						NR			
Rosenstock 2006 [510] NCT00086502	SAEs	Sitagliptin 100 + pioglitazone 30-45	Placebo + pioglitazone 30-45	0	175	0	178	0	175	0	178												
Green 2015 [391] NCT00790205	Fatal or non-fatal 1[ry] and 2[ry] outcome	Sitagliptin	Placebo	147	7257	159	7266	147	7257	159	7266			NR				31	7257	24		7266	
Shankar 2017 [605]	SAEs	Sitagliptin 100	Placebo	1	234	1	233	1	234	1	233			NR						NR			

NCT01590797																							
Vilsbøll 2010 [606] NCT00395343	SAEs	Sitagliptin 100mg + insulin ≥15IU ± metformin 1500	Placebo + insulin ≥15IU ± metformin 150	0	322	0	319	0	322	0	319			NR						NR		
Mathieu 2015 [607] NCT01462266	SAEs	Sitagliptin 100	Placebo	0	329	0	329	0	329	0	329			NR						NR		
Williams-Herman 2010 [608] NCT00103857	SAEs	Sitagliptin 100 Sitagliptin 1000 + metformin 100 Sitagliptin 1000 + metformin 2000 Sitagliptin 100 + metformin 2000	Metformin 1000 Metformin 2000 Placebo + metformin 2000	1	668	3	540	1 0 0 0	179 190 182 117	0 0 3	182 182 176			NR						NR		
Amin 2015 [609] NCT01059825	SAEs	Sitagliptin 100 Metformin	Placebo	0	55	0	429	0 0	55 375	0	54			NR						NR		
Aschner 2010 [610] NCT00449930	SAEs	Sitagliptin 100	Metformin 2000	0	528	0	522	0	528	0	522			NR						NR		
Olansky 2011 [611] NCT00482729	SAEs	Sitagliptin 100-200 + metformin 1000-2000[§]	Metformin 1000-2000	1	625	4	621	1	625	4	621			NR						NR		
Perez-Monteverde 2011 [612] NCT00541450	SAEs	Sitagliptin 100-200 + metformin 1000-2000[§]	Pioglitazone 30-45	0	224	0	248	0	224	0	248			NR						NR		
Wainstein 2012 [487] NCT00532935	SAEs	Sitagliptin 100-200 + metformin 1000-2000[§]	Pioglitazone	2	261	0	256	2	261	0	256			NR						NR		
Russel-Jones 2012 [613] NCT00676338	SAEs	Sitagliptin 100	Metformin Pioglitazone	0	163	1	409	0	163	1 0	246 163			NR						NR		
Raz 2006 [614] NCT00094757	SAEs	Sitagliptin 100 Sitagliptin 200	Placebo + pioglitazone	5	411	0	110	2 0	205 206	0	110	3 0	205 206	0	110					NR		
NCT01076075 [509]	SAEs	Sitagliptin 100	Placebo + pioglitazone 30	1	210	0	212	1	210	0	212			NR						NR		
Hermansen 2007 [615] NCT00106704	SAEs	Sitagliptin 100	Placebo	2	222	1	219	2	222	1	219			NR						NR		
Yoon 2012 [507] NCT01028391	SAEs	Sitagliptin 100 + pioglitazone 45	Pioglitazone 45	0	164	1	153	0	164	1	153			NR						NR		
Yoon 2011 [507] NCT00397631	SAEs	Sitagliptin 100 + pioglitazone 45	Pioglitazone 45	0	164	2	153	0	164	2	153			NR						NR		
Bergenstal 2010 [616] NCT00637273	SAEs	Sitagliptin 100	Pioglitazone 45	1	166	1	165	1	166	1	165			NR						NR		
NCT00722371 [474]	SAEs	Sitagliptin 100 Sitagliptin 100 + pioglitazone 15 Sitagliptin 100 + pioglitazone 30 Sitagliptin 100 + pioglitazone 45	Pioglitazone 15 Pioglitazone 30 Pioglitazone 45	3	922	2	693	1 0 1 0	231 230 231 230	1 1 0	230 233 230	0 1 0 0	231 230 231 230	0 0 0	230 233 230					NR		
Chan 2008 [617] NCT00095056	SAEs	Sitagliptin 25	Placebo + glipizide 5-20	2	65	1	26	2	65	1	26			NR						NR		
Charbonnel 2006 [512] NCT00086515	SAEs	Sitagliptin 100	Placebo + glipizide 5	3	464	1	237	0	464	1	237	3	464	0	237							
Ahrén 2014 [618] NCT00838903	SAEs	Sitagliptin 100	Placebo Glimepiride 2	0	302	2	408	0	302	1 0	101 307	0	302	1 0	101 307					NR		
Arjona Ferreira 2013 [619] NCT00509236	SAEs	Sitagliptin 25	Glipizide 2.5-10	0	64	0	65	0	64	0	65			NR						NR		
Ferreira 2013 [620] NCT00509262	SAEs	Sitagliptin 25-50	Glipizide 2.5-20	5	210	4	212	4	210	3	212	1	210	1	212	1	210		1	212		
Seck 2010 [621] NCT00094770	SAEs	Sitagliptin 100 + metformin >1500	Glipizide 5-20 + metformin >1500	0	588	1	584	0	588	1	584			NR						NR		
Arechavaleta 2011 [622] NCT00701090	SAEs	Sitagliptin 100	Glimepiride 1-6	0	516	3	518	0	516	2	518	0	516	1	518	0	516		1	518		
NCT01131182 [623]	SAEs	Sitagliptin 100	Sulfonylurea	0	507	1	514	0	507	1	514			NR						NR		
Terauchi 2017 [624] NCT01183104	SAEs	Sitagliptin 50	Glimepiride 0.5	1	148	0	143	1	148	0	143			NR						NR		
Leiter 2014 [625] NCT01098539	SAEs	Sitagliptin 30-50	Albiglutide 30-50	6	246	2	249	5	246	2	249	1	246	0	249	1	246		0	249		
Pratley 2011 [626] NCT00700817	SAEs	Sitagliptin 100	Liraglutide 1.2 Liraglutide 1.8	0	219	0	439	0	219	0 0	221 218			NR						NR		
Zang 2016 [627]	SAEs	Sitagliptin 100	Liraglutide 1.8	1	184	0	183	1	184	0	183			NR						NR		

NCT02008682																							
NCT01519674 [628]	SAEs	Sitagliptin + biphasic insulin aspart	Biphasic insulin aspart	2	383	0	192	1	383	0	192	1 0	190 193	0	192			NR					
Philis-Tsimikas 2013 [515] NCT01046110	SAEs	Sitagliptin 100	Insuline degludec 100IU	2	228	1	226	2	228	1	226			NR				NR					
NCT00875394 [629]	SAEs	Sitagliptin 100 + metformin	Metformin + any non-DPP4-Is Metformin	0	36	0	32	0 0	36 23	0	9			NR				NR					
Vildagliptin therapy																							
NCT00646542 [630]	SAEs	Vildagliptin 50	Placebo	0	292	0	227	0	292	0	227			NR				NR					
NCT00821977 [631]	SAEs	Vildagliptin	Placebo	0	301	0	150	0	301	0	150							NR					
Scherbaum 2008 [632] NCT00300287	SAEs	Vildagliptin 50	Placebo	0	156	1	150	0	156	1	150			NR				NR					
Dejager 2007 [633] NCT00099905	SAEs	Vildagliptin 50 Vildagliptin 100	Placebo	1	472	0	160	0 1	236 236	0	160			NR				NR					
McMurray 2013 [634] NCT00894868	SAEs	Vildagliptin 100	Placebo	1	128	4	126	1	128	4	126			NR				NR					
Pan 2012 [635] NCT00822211	SAEs	Vildagliptin 50 Vildagliptin 100	Placebo	0	294	1	144	0 0	148 146	1	144			NR				NR					
CLAF237ADE02 [636]	SAEs	Vildagliptin 100	Placebo	0	268	0	134	0	268	0	134							NR					
Bosi 2007 [637] NCT00099892	SAEs	Vildagliptin 50 Vildagliptin 100	Placebo	1	360	1	181	0 1	177 183	1	181			NR				NR					
Yang 2015 [638] NCT01357252	SAEs	Vildagliptin 50	Placebo	0	143	1	135	0	143	1	135			NR				NR					
Garber 2008 [639] NCT00099944	SAEs	Vildagliptin 50 Vildagliptin 100	Placebo	0	339	0	176	0 0	170 169	0	113			NR				NR					
Fonseca 2009 [640] NCT00099931	SAEs	Vildagliptin 100	Placebo	0	144	0	152	0	144	0	152			NR				NR					
Bosi 2009 [641] NCT00468039	SAEs	Vildagliptin 100 Vildagliptin 100 + metformin 1000 Vildagliptin 100 + metformin 2000	Metformin 1000	0	879	0	292	0 0 0	297 290 292	0	292			NR				NR					
Schweizer 2007 [642] NCT00099866	SAEs	Vildagliptin 100	Metformin 2000	1	511	0	249	1	511	0	249			NR				NR					
Pan 2008 [643] NCT00110240	SAEs	Vildagliptin 100	Placebo	0	440	0	220	0	440	0	220			NR				NR					
Rosenstock 2009 [644] NCT00138619	SAEs	Vildagliptin 100	Rosiglitazone 8	3	393	0	198	3	393	0	198			NR					1	393	0	198	
Bolli 2009 [645] NCT00237237	SAEs	Vildagliptin 100	Pioglitazone 30	2	295	3	280	2	295	3	280			NR				NR					
Foley 2009 [646] NCT00102388	SAEs	Vildagliptin 100	Gliclazide 320	3	546	0	546	3	546	0	546			NR				NR					
Ferrannini 2009 [647] NCT00106340	SAEs	Vildagliptin 100	Glimepiride 2	0	1389	7	1383	0	1389	7	1383			NR				NR					

Abbreviations: *AEs*, adverse events; *AHG*, *anti-* hyperglycaemic drugs; *NR*, not report; *SAEs*, serious adverse events; *VS.*, versus.
Note: ¶ Novel treatment of fixed-dose combination of 2 different class of AHG.

3.6.2 GLP1-RAs therapies

Supplemental Table 3-8. Studies results of stroke outcomes with GLP1-RAs therapies

Study Trial registry	Type of stroke index event	Intervention of interest		Number of strokes				Ischaemic stroke				Haemorrhagic stroke				Fatal stroke			
		GLP1-RAs (mg/day)	Controls (mg/day)	GLP1-RAs		Controls		GLP1-RAs		Controls		GLP1-RAs		Controls		GLP1-RAs		Controls	
				Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size
Albiglutide therapy																			
Nauck 2016 [648] NCT00849017	SAEs	Albiglutide 30 Albiglutide 50	Placebo	3	200	3	101	3	200	3	101			NR				NR	
Hernandez 2018 [392] NCT02465515	Fatal or non-fatal 2[ry] outcome	Albiglutide 30 Albiglutide 50	Placebo	94	4731	108	4732	94	4731	108	4732			NR		18	4731	17	4732
Reusch 2014 [649] NCT00849056	SAEs	Albiglutide 30	Placebo	0	150	0	151	0	150	0	151			NR				NR	
Nauck 2016 [648] NCT00839527	SAEs	Albiglutide 30 Albiglutide 50	Placebo	3	200	3	101	3	200	3	101			NR				NR	
Seino 2014 [650] NCT01098461	SAEs	Albiglutide 30 Albiglutide 50	Placebo	0	200	1	101	0	200	1	101			NR				NR	
Ahrén 2017 [618] NCT00838903	SAEs	Albiglutide 30 + metformin	Placebo + metformin Glimepiride 2 + metformin	3	302	2	408	2	302	2	408	0 1	302 101	0	307			NR	
Home 2014 [472] NCT00839527	SAEs	Albiglutide 30	Pioglitazone Placebo	1	271	8	392	0	271	8	392	0 1	271 277	0	392			NR	
Pratley 2014 [651] NCT01128894	SAEs	Albiglutide 50	Liraglutide 1.8	3	404	1	408	3	404	1	408			NR				NR	
Weissman 2014 [652] NCT00838916	SAEs	Albiglutide 30	Insulin glargine	4	504	0	241	4	504	0	241			NR				NR	
Rosenstock 2014 [653] NCT00976391	SAEs	Albiglutide 50 + insulin glargine	Insulin lispro 4-8 IU + insulin glargine	0	285	0	281	0	285	0	281			NR				NR	
Dulaglutide therapy																			
Gerstein 2019 [400] NCT01394952	Fatal or non-fatal 1[ry] outcome	Dulaglutide 1.5	Placebo	158	4949	205	4952	135	4949	175	4952			NR		26	4949	33	4952
Wysham 2014 [523] NCT01064687	SAEs	Dulaglutide 0.75 Dulaglutide 1.5	Placebo	1	559	0	141	1	559	0	141			NR				NR	
Pozzilli 2017 [654] NCT02152371	SAEs	Dulaglutide 1.5	Placebo	3	150	0	150	3	150	0	150			NR				NR	
Exenatide therapy																			
Holman 2017 [393] NCT01144338	Fatal or non-fatal 1[ry] and 2[ry] outcome	Exenatide 2	Placebo	187	7356	218	7396	187	7356	218	7396			NR		18	7356	25	7396
Gao 2009 [655] NCT00324363	SAEs	Exenatide 10-20µg	Placebo	0	234	1	232	0	234	1	232			NR				NR	
Gill 2010 [656] NCT00516074	SAEs	Exenatide 5-10µg Placebo	Placebo	0	28	0	26	0	28	0	26			NR				NR	
NCT00603239 [657]	SAEs	Exenatide 10-20µg Placebo	Placebo	1	111	0	54	1	111	0	54			NR				NR	
Wysham 2014 [523] NCT01064687	SAEs	Exenatide 10-20µg Placebo	Placebo	0	276	0	141	0	276	0	141			NR				NR	
Gadde 2017 [600] NCT01652729	SAEs	Exenatide 2µg Placebo	Placebo	1	181	0	61	1	181	0	61			NR				NR	
Gallwitz 2012 [658] NCT00359762	SAEs	Exenatide 10-50µg Exenatide + TZDs Exenatide + glimepiride 1	Glimepiride	3	827	0	508	3	827	0	508			NR				NR	

Buse 2013 [659] NCT01029886	SAEs	Exenatide 2µg	Liraglutide 1.8	1	461	2	450	1	461	2	450			NR			0	461	1	450
Russel-Jones 2012 [613] NCT00676338	SAEs	Exenatide 2µg	Metformin Pioglitazone	0	248	1	409	0	248	1	409			NR					NR	
Bergenstal 2010 [616] NCT00637273	SAEs	Exenatide 100µg	Pioglitazone 45	0	160	1	165	0	160	1	165			NR					NR	
Nauck 2007 [660] NCT00082407	SAEs	Exenatide 5-10µg	Insulin aspart	0	253	1	248	0	253	1	248			NR					NR	
Inagaki 2012 [661] NCT00935532	SAEs	Exenatide 2µg	Insulin glargine 4 IU	1	215	0	212	1	215	0	212			NR					NR	
Liraglutide therapy																				
Marso 2016 [394] NCT01179048	Fatal and non-fatal 1[ry] and 2[ry] outcome	Liraglutide	Placebo	173	4668	199	4672	159	4668	177	4672			NR			16	4668	25	4672
Seino 2016 [662] NCT01572740	SAEs	Liraglutide	Placebo	1	127	1	130	1	127	1	130			NR					NR	
Kaku 2011 [663] NCT00393718	SAEs	Liraglutide 0.9µg	Glibenclamide	0	268	2	132	0	268	2	132			NR					NR	
Bailey 2016 [664] NCT01907854	SAEs	Liraglutide 0.6-1.8µg	Sitagliptin 100	0	202	1	204	0	202	1	204			NR					NR	
Lingvay 2016 [665] NCT01952145	SAEs	Liraglutide 0.6µg/insulin degludec 16 units	Insulin degludec 16 units	1	278	2	279	1	278	1	279	0	278	1	279	0	278	1	279
NCT01117350 [666]	SAEs	Liraglutide 0.6-1.8µg	Insulin glargine	2	481	3	644	2	481	3	644			NR					NR	
Lixisenatide therapy																				
Pfeffer 2015 [395] NCT01147250	Fatal and non-fatal 1[ry] and 2[ry] outcome	Lixisenatide	Placebo	54	3034	49	3034	54	3034	49	3034			NR					NR	
Semaglutide therapy																				
Marso 2016 [401] NCT01720446	Non-fatal 1[ry] and 2[ry] outcome	Semaglutide	Placebo	27	1648	44	1649	25	1648	37	1649	2	1648	4	1649			NR		
Husain 2019 [396] NCT02692716	Non-fatal 1[ry] and 2[ry] outcome	Semaglutide	Placebo	12	1591	16	1592	12	1591	16	1592			NR					NR	
Taspoglutide therapy																				
Raz 2012 [667] NCT00744926	SAEs	Taspoglutide 10 Taspoglutide 20	Placebo	1	245	0	90	1	245	0	90			NR					NR	
NCT01018173 [668]	SAEs	Taspoglutide 10 Taspoglutide 20	Placebo	0	1059	0	1059	0		0				NR					NR	
Bergenstal 2012 [599] NCT00754988	SAEs	Taspoglutide 10 Taspoglutide 20	Placebo	0	379	0	90	0	379	0	90			NR					NR	
Hollander 2012 [669] NCT00823992	SAEs	Taspoglutide 20	Placebo	0	154	0	150	0	154	0	150			NR					NR	
Henry 2012 [670] NCT00744367	SAEs	Taspoglutide 10 Taspoglutide 20	Placebo	0	223	1	101	0	223	1	101			NR					NR	
Pratley 2012 [671] NCT00909597	AEs	Taspoglutide 10 Taspoglutide 20	Placebo Pioglitazone	0	494	0	257	0	494	0	257			NR					NR	
Rosenstock 2013 [672] NCT00717457	Non-fatal 1[ry] and 2[ry] outcome	Taspoglutide 10 Taspoglutide 20	Exenatide 20µg	2	788	0	385	1	788	0	385	1 0	394 394	0	385	1 0	394 394	0	385
Nauck 2013 [673] NCT00755287	SAEs	Taspoglutide 10 Taspoglutide 20	Insulin glargine 10 IU	0	715	0	322	0	715	0	322			NR					NR	

Abbreviations: *AEs*, adverse events; *AHG*, *anti-* hyperglycaemic drugs; *NR*, not report; *SAEs*, serious adverse events; *VS.*, versus.

Note: ¶novel treatment of fixed-dose combination of 2 different class of AHG.

3.6.3 SGLT2-Is therapies

Supplemental Table 3-9. Studies results of stroke outcomes with SGLT2-Is therapies

Study Trial registry	Type of stroke index event	Intervention of interest		Number of strokes				Ischaemic stroke				Haemorrhagic stroke				Fatal stroke			
		SGLT2-Is (mg/day)	Controls (mg/day)	SGLT2-Is		Controls		SGLT2-Is		Controls		SGLT2-Is		Controls		SGLT2-Is		Controls	
				Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size	Event	Sample size
Canagliflozin therapy																			
Inagaki 2013 [674] NCT01022112	SAEs	Canagliflozin 50 Canagliflozin 100 Canagliflozin 200 Canagliflozin 300	Placebo	0	307	0	75	0 0	82 74 76 75	0	75			NR				NR	
Inagaki 2014 [675] NCT01413204	SAEs	Canagliflozin 100 Canagliflozin 200	Placebo	0	179	0	93	0	90 89	0	93			NR				NR	
Stenlöf 2012 [676] NCT01081834	SAEs	Canagliflozin 100 Canagliflozin 200	Placebo	0	392	2	192	0	392	1	192	0 0	195 197	1	192			NR	
Weir 2014 [677] NCT01064414	SAEs	Canagliflozin 100 Canagliflozin 200	Placebo	3	358	1	78	1 2	80 178	1	78			NR				NR	
Sha 2014 [678] NCT01483781	SAEs	Canagliflozin 300	Placebo	0	17	0	18	0	17	0	18			NR				NR	
Qiu 2014 [679] NCT01340664	SAEs	Canagliflozin 50 Canagliflozin 150	Placebo	0	186	0	93	0	93 93	0	93			NR				NR	
Rosenstock 2012 [601] NCT00642278	SAEs	Canagliflozin 50 Canagliflozin 100 Canagliflozin 200 Canagliflozin 300 Canagliflozin 600	Placebo	0	321	0	65	0 0 0 0 0	64 64 65 64 64	0	65			NR				NR	
Ji 2015 [680] NCT01381900	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo	1	450	1	226	1 0	223 227	1	226			NR				NR	
Wilding 2013 [681] NCT01106625	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo	1	313	0	156	1	157 156	0	156			NR				NR	
Fulcher 2015 [682] NCT01032629	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo	0	82	0	45	0 0	42 40	0	45			NR				NR	
Cai 2018 [683] NCT02025907	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo	0	108	2	108	0	108	2	108			NR				NR	
Bode 2015 [525] NCT01106651	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo	5	208	0	104	4 1	104 104	0	104			NR				NR	
Lavalle-González 2013 [684] NCT01106677	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo Sitagliptin 100 + placebo	4	735	1	549	2 2	368 367	1 0	366 183			NR				NR	
Forst 2014 [513] NCT01106690	SAEs	Canagliflozin 100 Canagliflozin 300	Placebo + sitagliptin 100	1	227	0	115	0 1	113 114	0	115			NR				NR	
Rosenstock 2016 [685] NCT01809327	SAEs	Canagliflozin 100 Canagliflozin 300 Canagliflozin 100 + metformin Canagliflozin 300 + metformin	Metformin	2	949	0	237	0 1 0 1	237 238 237 237	0	237			NR				NR	
Cefalu 2013 [686] NCT00968812	SAEs	Canagliflozin 100 Canagliflozin 300	Glimepiride	9	968	3	482	3 5	483 485	3	482	0 1	483 485	0	482			NR	
Schernthaner 2013 [687] NCT01137812	SAEs	Canagliflozin 300	Sitagliptin 100	1	377	1	378	1	377	1	378			NR				NR	
Dapagliflozin therapy																			
Wiviott 2019 [397] NCT01730534	Non-fatal 1^{ry} and 2^{ry} outcome	Dapagliflozin 5	Placebo	235	8582	231	8578	235	8582	231	8578			NR				NR	
Kaku 2013 [688]	SAEs	Dapagliflozin 1	Placebo	0	225	0	54	0	59	0	54			NR				NR	

NCT00972244		Dapagliflozin 2.5 Dapagliflozin 5 Dapagliflozin 10						0 0 0	56 58 52										
Bailey 2012 [689] NCT00736879	SAEs	Dapagliflozin Dapagliflozin 2.5 Dapagliflozin 5	Placebo	0	214	0	68	0 0 0	72 74 68	0	68			NR				NR	
Kaku 2014 [690] NCT01294423	SAEs	Dapagliflozin 5 Dapagliflozin 10	Placebo	0	174	2	87	0 0	86 88	1	87	0 0	86 88	1	87			NR	
Bailey 2014 [691] NCT00528372	SAEs	Dapagliflozin 2.5 Dapagliflozin 5 Dapagliflozin 10	Placebo	1	199	0	75	1 0 0	165 64 70	0	75			NR				NR	
Schumm-Draeger 2015 [692] NCT01217892	SAEs	Dapagliflozin 5 + metformin Dapagliflozin 10 + metformin Dapagliflozin 10 + metformin	Placebo + metformin	0	299	0	101	0 0 0	100 100 99	0	101			NR				NR	
Bailey 2010 [693] NCT00528879	SAEs	Dapagliflozin 2.5 Dapagliflozin 5 Dapagliflozin 10	Placebo	1	409	2	137	1 0 0	137 137 135	2	137			NR				NR	
Bolinder 2014 [694] NCT00855166	SAEs	Dapaglilozin 10	Placebo	1	91	0	91	1	91	0	91			NR				NR	
Ji 2014 [695] NCT01095653	SAEs	Dapagliflozin 5 Dapagliflozin 10	Placebo	1	261	0	132	0 1	128 133	0	132			NR				NR	
Henry 2012 [696] (Study1) NCT00643851	SAEs	Dapagliflozin 5 Dapagliflozin 5 + metformin	Metformin + placebo	0	397	1	201	0 0	203 194	1	201			NR				NR	
Henry 2012 (Study2) [696] NCT00859898	SAEs	Dapagliflozin 10 Dapagliflozin 10 + metformin	Metformin + placebo	0	430	0	208	0	219 211	0	208			NR				NR	
Heerspink 2013 [697] NCT00976495	SAEs	Dapaglilozin 10	Placebo	0	24	0	25	0	24	0	25			NR				NR	
Matthaei 2015 [698] NCT01392677	SAEs	Dapaglilozin 10	Placebo	0	109	0	109	0	109	0	109			NR				NR	
Mathieu 2015 [607] NCT01646320	SAEs	Dapaglilozin 10	Placebo	0	160	0	160	0	160	0	160			NR				NR	
Jabbour 2014 [699] NCT00984867	SAEs	Dapaglilozin 10	Placebo	0	225	0	226	0	225	0	226			RN				NR	
Wilding 2012 [700] NCT00357370	SAEs	Dapagliflozin 10 + insulin Dapagliflozin 20 + insulin	Placebo	0	48	0	23	0	48	0	23			RN				NR	
Mudaliar 2014 [701]	SAEs	Dapaglilozin 5	Placebo	0	23	0	21	0	23	0	21			NR				NR	
NCT00831779 [702]	SAEs	Dapaglilozin 5	Placebo	0	23	0	21	0	23	0	21			NR				NR	
Strojek 2011 [703] NCT00680745	SAEs	Dapagliflozin 2.5 + insulin Dapagliflozin 5 + insulin Dapagliflozin 10 + insulin	Placebo	2	450	0	146	1 0 1	154 145 151	0	146			NR		0 0 1	154 145 151	0	146
Kohan 2014 [704] NCT00663260	SAEs	Dapagliflozin 5 Dapagliflozin 10	Placebo	1	168	0	84	0 1	83 85	0	84			NR				NR	
Rosenstock 2012 [526] NCT00683878	SAEs	Dapagliflozin 5 Dapagliflozin 10	Placebo	0	281	0	139	0	141 140	0	139			NR				NR	
Weber 2016 [705] NCT01195662	SAEs	Dapaglilozin 10	Placebo	0	225	0	224	0	225	0	224			NR				RN	
NCT01137474 [706]	SAEs	Dapagliflozin 2.5 Dapagliflozin 5 Dapagliflozin 10	Placebo	1	633	1	311	1 0 0	166 165 302	1	311			NR				NR	
Wilding 2014 [707] NCT00673231	SAEs	Dapagliflozin 2.5 Dapagliflozin 5 Dapagliflozin 10	Placebo	2	610	3	197	1 0 1	202 212 196	3	197			NR				NR	
Yang 2018 [708] NCT02096705	SAEs	Dapagliflozin 10	Placebo	1	139	0	133	1	139	0	133			NR				NR	
Cefalu 2015 [709] NCT01031680	SAEs	Dapagliflozin 10	Placebo	2	460	2	462	2	460	2	462			NR		0	460	1	462
Leiter 2014 [710] NCT01042977	SAEs	Dapagliflozin 10	Placebo	1	482	4	483	1	482	4	483			NR				NR	
List 2009 [711] NCT00263276	SAEs	Dapagliflozin 2.5 Dapagliflozin 5	Placebo Metformin	0	253	0	106	0 0	53 55	0 0	55 51			NR				NR	

		Dapagliflozin 10 Dapagliflozin 20 Dapagliflozin 50						0 0 0	40 55 50										
Nauck 2014 [712] NCT00660907	SAEs	Dapagliflozin 10 + metformin	Glipizide 20 + metformin	2	406	0	408	2	406	0	408			NR				NR	
Rosenstock 2015 [713] NCT01606007	SAEs	Dapagliflozin 10 + saxagliptin 10 + metformin Dapagliflozin 10 + metformin	Saxagliptin 5 + metformin	1	358	0	176	1	358	0	176			NR				NR	
Empagliflozin therapy																			
Kadowaki 2015 [714] NCT01193218	SAEs	Empagliflozin 5 Empagliflozin 10 Empagliflozin 25 Empagliflozin 50	Placebo	1	752	0	109	0 0 1 0	110 267 265 110	0	109			NR				NR	
NCT01649297 [715]	SAEs	Empagliflozin 5 Empagliflozin 10 Empagliflozin 12.5 Empagliflozin 25	Placebo	2	876	1	107	0 0 0 2	219 220 219 213	1	107			NR				NR	
Merker 2015 [716] NCT01289990; NCT01159600	Non-fatal 1^{ry} and 2^{ry} outcome	Empagliflozin 10 Empagliflozin 25	Placebo	1	430	0	207	0 1	217 213	0	207			NR				NR	
Ha¨ring 2013 [717] NCT01159600	SAEs	Empagliflozin 10 Empagliflozin 25 Empagliflozin 25 (open-label)	Placebo	1	359	0	141	1 0 0	152 139 68	0	141			NR				NR	
Rosenstock 2015 [718] NCT01011868	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	5	324	1	170	1 3	169 155	0	170	1 0	169 155	1	170			NR	
Zinman 2015 [398] NCT01131676	Fatal and non-fatal 1^{ry} and 2^{ry} outcome	Empagliflozin 10 Empagliflozin 25	Placebo	164	4687	69	2333	150	4687	60	2333			NR			14	4687	9	2333
Barnett 2014 [676] NCT01164501	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	5	419	3	319	0 5	98 321	3	319			NR				NR	
Rosenstock 2014 [719] NCT01306214	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	1	375	1	188	1 0	186 189	1	188			NR				NR	
Kovacs 2014 [514] NCT01210001	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	1	333	0	165	0 1	165 168	0	165			NR				NR	
Kovacs 2014 [514] NCT01289990	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	0	333	2	165	0 0	165 168	2	165			NR				NR	
Tikkanen 2015 [720] NCT01370005	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	0	552	0	272	0 0	276 276	0	272			NR				NR	
Ferrannini 2013 [721] NCT00789035	SAEs	Empagliflozin 5 Empagliflozin 10 Empagliflozin 25	Placebo	0	244	0	162	0 0 0	81 81 82	0	162			NR				NR	
Roden 2013 [593] NCT01177813	SAEs	Empagliflozin 10 Empagliflozin 25 Empagliflozin 25	Placebo	1	534	1	229	1 0 0	224 223 87	1	229			NR				NR	
Søfteland 2017 [550] NCT01734785	SAEs	Empagliflozin 10 Empagliflozin 25	Placebo	0	222	0	110	0	112 110	0	110			NR				NR	
Rosenstock 2013 [602] NCT00749190	SAEs	Empagliflozin 1 Empagliflozin 5 Empagliflozin 10 Empagliflozin 25 Empagliflozin 50	Placebo	0	136	0	26	0 0 0 0 0	21 26 30 25 34	0	26			NR				NR	
Ferrannini 2013 [721] (Study 1) NCT00881530	SAEs	Empagliflozin 10 Empagliflozin 25	Metformin	1	215	0	56	1 0	106 109	0	56			NR				NR	
Hadjadj 2016 [722] NCT01719003	SAEs	Empagliflozin 10 Empagliflozin 25 Empagliflozin 10 + metformin 1000 Empagliflozin 10 + metformin 2000 Empagliflozin 2 + metformin 1000 Empagliflozin 25 + metformin 2000 Empagliflozin 25+ metformin	Metformin 1000 Metformin 2000	1	1032	1	341	0 0 0 0 0 1 0	172 167 129 171 170 170 53	0 1	171 170			NR				NR	

Araki 2015 [503] NCT01368081	SAEs	Empagliflozin 10 + sulfonylurea Empagliflozin 25 + sulfonylurea Empagliflozin 10 + glinide Empagliflozin 25 + glinide Empagliflozin 10 + biguanide Empagliflozin 25 + biguanide Empagliflozin 10 + TZDs Empagliflozin 25 + TZDs Empagliflozin 10 + α-glucosidase-Is Empagliflozin 25 + α-glucosidase-Is Empagliflozin 10 + DPP4-Is Empagliflozin 25 + DPP4-Is	Metformin	3	1097	0	63	0 0 0 0 0 0 1 1 0 0 1 0	136 137 70 70 68 65 137 136 69 70 68 71	0	63			NR			NR
Ridderstra°le 2014 [723] NCT01167881	SAEs	Empagliflozin 25	Glimepiride 1-4mg	14	765	15	780	14	765	12	780	0	765	3	780	NR
DeFronzo 2015 [724] NCT01422876	SAEs	Empagliflozin 10 Empagliflozin 25 Empagliflozin 10 + linagliptin 5 Empagliflozin 25 + linagliptin 5	Linagliptin 5	6	546	1	128	2 0 2 1	137 140 135 134	1	128	0 0 1 0	137 140 135 134	0	128	NR
Ferrannini 2013 [721] (Study 2) NCT00881530	SAEs	Empagliflozin 10 Empagliflozin 25	Sitagliptin	3	332	3	56	1 2	166 166	3	56			NR		NR
Ertugliflozin therapy																
Dagogo-Jack 2018 [725] NCT02036515	SAEs	Ertugliflozin 5 Ertugliflozin 15	Placebo	2	309	0	153	1	156 153	0	153	0 1	156 153	0	153	NR
Miller 2018 [726] NCT02226003	SAEs	Ertugliflozin 5 + sitagliptin 100 Ertugliflozin 15 + sitagliptin 100	Placebo	0	219	0	429	0 0	98 96	1	97			NR		NR
Amin 2015 [609] NCT01059825	SAEs	Ertugliflozin 1 Ertugliflozin 5 Ertugliflozin 10 Ertugliflozin 25	Placebo Metformin	0	194	1	97	0 0 0 0	54 55 55 55	0 0	54 375			NR		NR
Ipragliflozin therapy																
Wilding 2013 [727] NCT01117584	SAEs	Ipragliflozin 12.5 Ipragliflozin 50 Ipragliflozin 150 Ipragliflozin 300	Placebo	0	276	0	66	0 0 0 0	69 68 67 72	0	66			NR		NR
Kashiwagi 2015 [728] NCT01135433	SAEs	Ipragliflozin 50	Placebo	0	112	0	56	0	112	0	56			NR		NR
Lu 2016 [729] NCT01505426	SAEs	Ipragliflozin	Placebo	0	87	0	83	0	87	0	83			NR		NR

Abbreviations: *AEs*, adverse events; *AHG*, *anti*- hyperglycaemic drugs; *NR*, not report; *SAEs*, serious adverse events; *vs*., versus.

Note: ¶novel treatment of fixed-dose combination of 2 different class of AHG.

3.7 Meta-analyses GRADE outcomes

3.7.1 DPP4-Is class

3.7.1.1 DPP4-Is and non-fatal stroke by subtypes

Supplemental Table 3-10. GRADE evidence profile of DPP4-Is and non-fatal stroke by subtypes

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With DPP4-Is		Risk with placebo / controls	Risk difference with DPP4-Is
DPP4-Is non-fatal stroke by subtypes and treatment allocation (follow-up: range 4-432 weeks)											
125083 (95 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	662/56471 (1.2%)	652/68612 (1.0%)	RR 0.91 (0.82 to 1.01)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic stroke DPP4-Is vs. placebo (follow-up: range 4-224 weeks)											
65549 (44 RCTs)	not serious	not serious	not serious	serious[b]	none	⊕⊕⊕◯ MODERATE	476/30895 (1.5%)	470/34654 (1.4%)	RR 0.95 (0.84 to 1.07)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic stroke DPP4-Is vs. placebo (follow-up: range 24-76 weeks)											
3962 (6 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	5/1849 (0.3%)	3/2113 (0.1%)	RR 0.68 (0.22 to 2.12)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic stroke DPP4-Is vs. AHGs (follow-up: range 4-432 weeks)											
43694 (51 RCTs)	serious[a]	not serious	not serious	serious[d]	none	⊕⊕◯◯ LOW	177/19168 (0.9%)	165/24526 (0.7%)	RR 0.82 (0.67 to 1.01)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic stroke DPP4-Is vs. AHGs (follow-up: range 24-162 weeks)											
11878 (13 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	4/4559 (0.1%)	15/7319 (0.2%)	RR 1.28 (0.57 to 2.87)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **DPP4-I:** dipeptidyl peptidase-4 inhibitors; **RR:** Risk ratio.

3.7.1.1.1 GRADE evidence

a. Ten studies that carried small weight DPP4-Is vs. AHGs (ischaemic stroke (0.4%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) and (haemorrhagic stroke (0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (95), in which 6 studies were unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.38). However, all studies reported an overlap CIs, in which (20) studies reported wide CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (945) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.51). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for small benefit not exceeding a minimal important difference, including only (8) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (P=0.06). However, all studies reported an overlap CIs, in which (21) studies reported wide CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (342) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.54). However, all studies reported an overlap CIs, in which (11) studies reported wide CIs. The 95% CI was consistent with the possibility for small benefit not exceeding a minimal important difference, including only (17) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (P=0.50). However, the majority of studies reported an overlap CIs, in which (55) reported wide CIs. The small study (1.5%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of DPP4-Is favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,313) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=1.00; I^2=0%) or a subgroup difference (P=0.52; I^2=0%). Majority of studies at low risk of bias (98.5%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 10 studies with open-label design out of 95. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.1.2 DPP4-Is and fatal stroke

Supplemental Table 3-11. GRADE evidence profile of DPP4-Is and fatal stroke

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With DPP4-Is		Risk with placebo / controls	Risk difference with DPP4-Is
DPP4-Is fatal stroke (follow-up: range 4-224 weeks)											
47427 (9 RCTs)	not serious	not serious	not serious	very serious[a]	none	⊕⊕◯◯ LOW	93/23580 (0.4%)	87/23847 (0.4%)	RR 0.93 (0.69 to 1.24)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic fatal stroke DPP4-Is vs. placebo (follow-up: range 109-224 weeks)											
37994 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	75/18963 (0.4%)	70/19031 (0.4%)	RR 0.93 (0.67 to 1.29)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic fatal stroke DPP4-Is vs. AHGs (follow-up: range 52-432 weeks)											
7482 (3 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	16/3638 (0.4%)	15/3844 (0.4%)	RR 0.90 (0.45 to 1.79)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic fatal stroke DPP4-Is vs. AHGs (follow-up: range 30-54 weeks)											
1951 (3 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	2/979 (0.2%)	2/972 (0.2%)	RR 1.01 (0.20 to 4.98)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **DPP4-I:** dipeptidyl peptidase-4 inhibitors; **RR:** Risk ratio.

3.7.1.2.1 GRADE evidence

a. The overall imprecision was precise without a significant effect difference (*P*=0.61). However, all studies reported an overlap CIs with narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (180) events with large sample size.

b. The overall imprecision was precise without a significant effect difference (*P*=0.66). However, all studies reported an overlap CIs with narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (145) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.76). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (31) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (*P*=0.99). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (4) events with small sample size.

In summary, the overall certainty of the pooled EE was with low precise imprecision without significant effect level of evidence difference (*P*=0.61). However, the majority of studies reported an overlap CIs, in which (4) reported wide CIs. All studies cross the line of no difference (1). The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including (180) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.71; I^2=0%) or a subgroup difference (*P*=0.99; I^2=0%). All studies at low risk of bias (100%). No evidence of detection or selection bias. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.1.3 DPP4-Is and stroke by baseline characteristics

Supplemental Table 3-12. GRADE evidence profile of DPP4-Is and stroke by baseline characteristics

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With DPP4-Is		Risk with placebo / controls	Risk difference with DPP4-Is
Risk of stroke in T2DM by baseline characteristics (follow-up: range 4-432 weeks)											
109243 (95 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	719/50063 (1.4%)	712/59180 (1.2%)	RR 0.93 (0.84 to 1.03)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM DPP4-Is vs. placebo (follow-up: range 4-206 weeks)											
17856 (34 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	33/7057 (0.5%)	39/10799 (0.4%)	RR 0.74 (0.50 to 1.11)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM DPP4-Is vs. AHGs (follow-up: range 4-104 weeks)											
35102 (44 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	5/1849 (0.3%)	3/2113 (0.1%)	RR 0.68 (0.22 to 2.12)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM and CVD DPP4-Is vs. placebo (follow-up: range 12-157 weeks)											
40912 (6 RCTs)	not serious	not serious	not serious	serious[d]	none	⊕⊕⊕◯ MODERATE	177/19168 (0.9%)	165/24526 (0.7%)	RR 0.82 (0.67 to 1.01)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM and CVD DPP4-Is vs. AHGs (follow-up: range 104-432 weeks)											
6355 (2 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	4/5142 (0.1%)	13/7830 (0.2%)	RR 1.29 (0.58 to 2.90)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM and CKD DPP4-Is vs. placebo (follow-up: range 24-224 weeks)											
7775 (5 RCTs)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ LOW	94/3878 (2.4%)	85/3897 (2.2%)	RR 0.90 (0.67 to 1.20)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Risk of stroke in T2DM and CKD DPP4-Is vs. AHGs (follow-up: range 52-54 weeks)											
1243 (4 RCTs)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	9/609 (1.5%)	14/634 (2.2%)	RR 1.42 (0.62 to 3.25)	1 per 100	1 more per 100 (from 1 fewer to 3 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CVD:** cardiovascular disease; **CI:** Confidence interval; **CKD:** chronic kidney disease; **DPP4-I:** dipeptidyl peptidase-4 inhibitors; **RR:** Risk ratio; **T2DM:** type 2 diabetes mellitus.

3.7.1.3.1 GRADE evidence

a. Eight studies that carried small weight DPP4-Is vs. AHGs (in T2DM (0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) and (in T2DM with CVD (0.3%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (95), in which 4 studies were unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.14). However, all studies reported an overlap CIs, in which (17) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (72) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.09). However, all studies reported an overlap CIs, in which (19) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (139) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (P=0.92). However, all studies reported an overlap CIs, in which one study reported wide CI. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (792) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.21). However, all studies reported narrow and overlap CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (226) events with large sample size.

f. The overall imprecision was precise without a significant effect difference (P=0.48). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (179) events with large sample size.

g. The overall imprecision was precise without a significant effect difference (P=0.41). However, all studies reported an overlap CIs, in which one study reported a wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (23) events with small sample size (1,243).

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (P=0.14). However, the majority of studies reported an overlap CIs, in which (41) reported wide CIs. The small study (1.4%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of DPP4-Is favour across active comparators in people with T2DM. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,431) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=1.00; I^2=0%) or a subgroup difference (P=0.34; I^2=11.9%). Majority of studies at low risk of bias (98.8%). No evidence of detection of bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, eight studies with open-

label design out of 95. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.1.4 DPP4-Is and stroke by clinical trial size

Supplemental Table 3-13. GRADE evidence profile of DPP4-Is and stroke by clinical trial size

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With DPP4-Is		Risk with placebo / controls	Risk difference with DPP4-Is
Risk of stroke risk by clinical trial size (follow-up: range 4-432 weeks)											
126177 (95 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	662/57054 (1.2%)	651/69123 (0.9%)	RR 0.92 (0.82 to 1.02)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Small RCTs DPP4-Is vs. placebo (follow-up: range 4-206 weeks)											
18727 (40 RCTs)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ LOW	44/7530 (0.6%)	45/11197 (0.4%)	RR 0.71 (0.49 to 1.02)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Large RCTs DPP4-Is vs. placebo (follow-up: range 78-224 weeks)											
47566 (5 RCTs)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ MODERATE	478/23742 (2.0%)	477/23824 (2.0%)	RR 1.00 (0.88 to 1.13)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Small RCTs DPP4-Is vs. AHGs (follow-up: range 4-104 weeks)											
31525 (47 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⨁◯◯◯ VERY LOW	67/13529 (0.5%)	76/17996 (0.4%)	RR 0.84 (0.61 to 1.15)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Large RCTs DPP4-Is vs. AHGs (follow-up: range 24-432 weeks)											
11425 (3 RCTs)	not serious	not serious	not serious	very serious[e]	none	⨁⨁◯◯ LOW	130/5262 (2.5%)	114/6163 (1.8%)	RR 0.84 (0.66 to 1.08)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **DPP4-I:** dipeptidyl peptidase-4 inhibitors; **RCTs:** randomise controlled trials; **RR:** Risk ratio.

3.7.1.4.1 GRADE evidence

a. Eight studies that carried small weight DPP4-Is vs. AHGs (small RCTs (0.3%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (95), in which 4 studies were unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (*P*=0.07). However, all studies reported an overlap CIs, in which (20) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (89) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.94). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (955) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (*P*=0.27). However, all studies reported an overlap CIs, in which (21) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (143) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (*P*=0.17). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (244) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (*P*=0.14). However, the majority of studies reported an overlap CIs, in which (41) reported wide CIs. The small study (1.4%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of DPP4-Is favour across active comparators in small RCTs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,431) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=1.00; I^2=0%) or a subgroup difference (*P*=0.23; I^2=29.8%). Majority of studies at low risk of bias (98.8%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, eight studies with open-label design out of 95. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.1.5 DPP4-Is and stroke by DPP4-Is by treatment allocation sub-class

Supplemental Table 3-14. GRADE evidence profile of DPP4-Is and stroke by DPP4-Is treatment allocation sub-class stratification

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With DPP4-Is		Risk with controls	Risk difference with DPP4-Is
Risk of stroke in T2DM by DPP4-Is treatment allocation sub-class (follow-up: range 4-432 weeks)											
109243 (95 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	719/50063 (1.4%)	712/59180 (1.2%)	RR 0.93 (0.84 to 1.03)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Alogliptin vs. placebo (follow-up: range 12-78 weeks)											
6816 (5 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	34/3239 (1.0%)	32/3577 (0.9%)	RR 0.88 (0.55 to 1.41)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Alogliptin vs. AHGs (follow-up: range 12-104 weeks)											
8454 (10 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	10/3009 (0.3%)	20/5445 (0.4%)	RR 0.95 (0.47 to 1.91)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Dutogliptin vs. placebo (follow-up: range 4-12 weeks)											
596 (2 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	2/127 (1.6%)	0/469 (0.0%)	RR 0.10 (0.01 to 0.90)	2 per 100	1 fewer per 100 (from 2 fewer to 0 fewer)
Linagliptin vs. placebo (follow-up: range 24-224 weeks)											
10112 (8 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	99/4779 (2.1%)	90/5333 (1.7%)	RR 0.89 (0.67 to 1.17)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Linagliptin vs. AHGs (follow-up: range 24-432 weeks)											
10749 (8 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⊕◯◯◯ VERY LOW	139/4808 (2.9%)	117/5941 (2.0%)	RR 0.80 (0.63 to 1.02)	3 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)
Omarigliptin vs. placebo (follow-up: mean 156 weeks)											
4192 (1 RCT)	not serious	not serious	not serious	very serious[g]	none	⊕⊕◯◯ LOW	34/2100 (1.6%)	32/2092 (1.5%)	RR 0.94 (0.59 to 1.53)	2 per 100	0 fewer per 100 (from 1 fewer to 1 more)
Omarigliptin vs. AHGs (follow-up: mean 24 weeks)											
642 (1 RCT)	not serious	not serious	not serious	very serious[h]	none	⊕⊕◯◯ LOW	2/320 (0.6%)	0/322 (0.0%)	RR 0.20 (0.01 to 4.12)	1 per 100	1 fewer per 100 (from 1 fewer to 2 more)
Saxagliptin vs. placebo (follow-up: range 24-206 weeks)											
21163 (10 RCTs)	not serious	not serious	not serious	serious[i]	none	⊕⊕⊕◯ MODERATE	149/9818 (1.5%)	172/11345 (1.5%)	RR 1.08 (0.87 to 1.34)	2 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Saxagliptin vs. AHGs (follow-up: range 18-104 weeks)											
3683 (4 RCTs)	not serious	not serious	not serious	very serious[j]	none	⊕⊕◯◯ LOW	8/1515 (0.5%)	8/2168 (0.4%)	RR 0.74 (0.28 to 1.97)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Sitagliptin vs. placebo (follow-up: range 12-157 weeks)											
20965 (13 RCTs)	not serious	not serious	not serious	serious[k]	none	⊕⊕⊕◯ MODERATE	196/10313 (1.9%)	193/10652 (1.8%)	RR 0.98 (0.81 to 1.20)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Sitagliptin vs. AHGs (follow-up: range 4-104 weeks)											
13632 (22 RCTs)	serious[a]	not serious	not serious	very serious[l]	none	⊕◯◯◯ VERY LOW	28/6483 (0.4%)	36/7149 (0.5%)	RR 1.05 (0.66 to 1.67)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Vildagliptin vs. placebo (follow-up: range 24-52 weeks)											
2449 (6 RCTs)	not serious	not serious	not serious	very serious[m]	none	⊕⊕◯◯ LOW	8/896 (0.9%)	3/1553 (0.2%)	RR 0.33 (0.11 to 1.04)	1 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)
Vildagliptin vs. AHGs (follow-up: range 52-104 weeks)											

Certainty assessment							Summary of findings				
5790 (5 RCTs)	not serious	not serious	not serious	very serious[n]	none	⨁⨁◯◯ LOW	10/2656 (0.4%)	9/3134 (0.3%)	RR 0.75 (0.32 to 1.77)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **DPP4-Is:** dipeptidyl peptidase-4 inhibitors; **RR:** Risk ratio.

3.7.1.5.1 GRADE evidence

a. Eight studies that carried small weight DPP4-Is vs. AHGs (0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (95), in which 4 studies were unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (*P*=0.60). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (66) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.89). However, all studies reported an overlap CIs, in which (5) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (30) events with large sample size.

d. The overall imprecision was precise with a significant effect difference (*P*=0.04). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with small sample size.

e. The overall imprecision was precise without a significant effect difference (*P*=0.39). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (189) events with large sample size.

f. The overall imprecision was precise with a significant effect difference (*P*=0.08). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (256) events with large sample size.

g. The overall imprecision was precise with a significant effect difference (*P*=0.82). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (66) events with large sample size.

h. The overall imprecision was precise with a significant effect difference (*P*=0.30). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with small sample size.

i. The overall imprecision was precise without a significant effect difference (*P*=0.50). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (321) events with large sample size.

j. The overall imprecision was precise without a significant effect difference (*P*=0.54). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (16) events with large sample size.

k. The overall imprecision was precise without a significant effect difference (*P*=0.86). However, all studies reported an overlap CIs, in which (8) studies reported wide CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (389) events with large sample size.

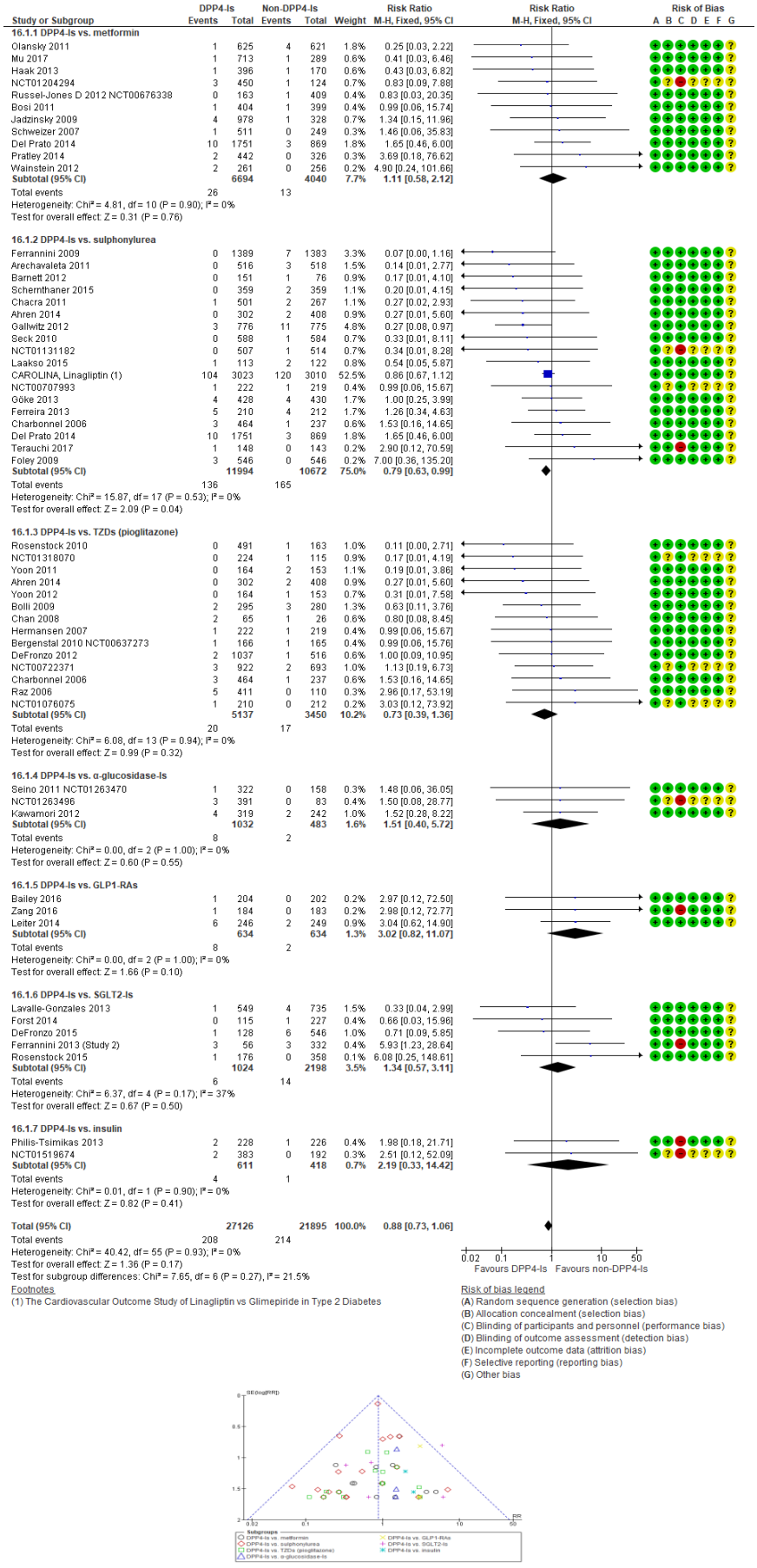
l. The overall imprecision was precise without a significant effect difference (*P*=0.84). However, all studies reported an overlap CIs, in which (12) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (64) events with large sample size.

m. The overall imprecision was precise without a significant effect difference (*P*=0.06). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (11) events with small sample size.

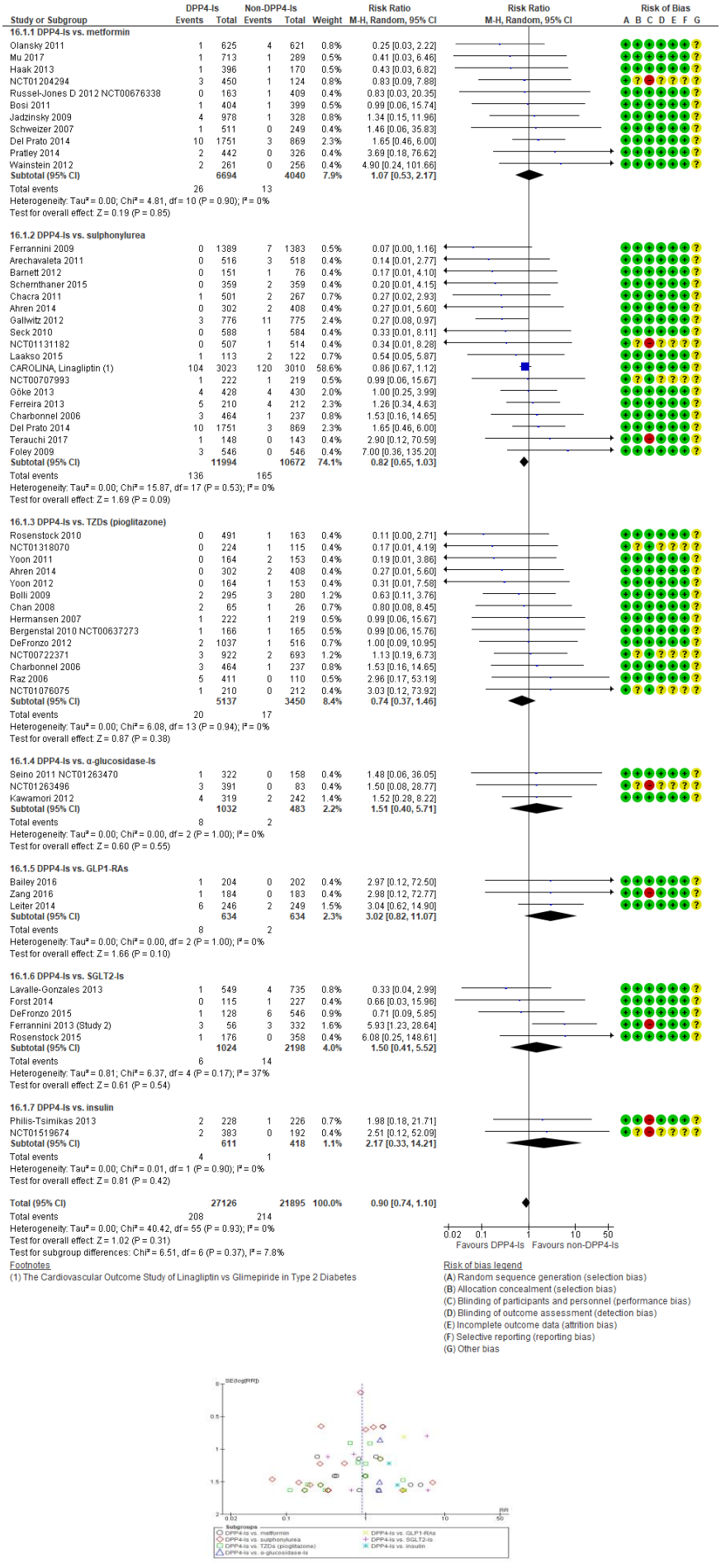
n. The overall imprecision was precise without a significant effect difference (*P*=0.51). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (19) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (*P*=0.14). However, the majority of studies reported an overlap CIs, in which (41) reported wide CIs. The small study (1.4%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of DPP4-Is favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,431) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=1.00; I^2=0%) or a subgroup difference (*P*=0.41; I^2=3.8%). Majority of studies at low risk of bias (99.0%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, eight studies with open-label design out of 95. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.1.6 DPP4-Is and stroke by AHGs sub-class



Supplemental Figure 3-2. Forest and funnel plot of DPP4-Is and stroke by DPP4-Is versus AHGs sub-class, Fixed-effect model.



Supplemental Figure 3-3. Forest and funnel plot of DPP4-Is and stroke by DPP4-Is versus AHGs sub-class, Random-effect model.

Supplemental Table 3-15. GRADE evidence profile of DPP4-Is and stroke by AHGs sub-class

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With DPP4-Is		Risk with controls	Risk difference with DPP4-Is
Risk of stroke in T2DM by DPP4-Is vs. AHGs sub-class (follow-up: range 4-432 weeks)											
49021 (53 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	214/21895 (1.0%)	208/27126 (0.8%)	RR 0.88 (0.73 to 1.06)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Metformin (follow-up: range 24-104 weeks)											
10734 (11 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ VERY LOW	13/4040 (0.3%)	26/6694 (0.4%)	RR 1.11 (0.58 to 2.12)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Sulfonylurea (follow-up: range 4-432 weeks)											
22666 (18 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ LOW	165/10672 (1.5%)	136/11994 (1.1%)	RR 0.79 (0.63 to 0.99)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
TZDs pioglitazone (follow-up: range 12-104 weeks)											
8587 (14 RCTs)	not serious	not serious	not serious	very serious[d]	none	⨁⨁◯◯ LOW	17/3450 (0.5%)	20/5137 (0.4%)	RR 0.73 (0.39 to 1.36)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
α-glucosidase-Is (follow-up: range 52-126 weeks)											
1515 (3 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⨁◯◯◯ VERY LOW	2/483 (0.4%)	8/1032 (0.8%)	RR 1.51 (0.40 to 5.72)	0 per 100	0 fewer per 100 (from 0 fewer to 2 more)
GLP1-RAs (follow-up: range 26-52 weeks)											
1268 (3 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⨁◯◯◯ VERY LOW	2/634 (0.3%)	8/634 (1.3%)	RR 3.02 (0.82 to 11.07)	0 per 100	1 more per 100 (from 0 fewer to 3 more)
SGLT2-Is (follow-up: range 24-52 weeks)											
3222 (5 RCTs)	serious[a]	not serious	not serious	very serious[g]	none	⨁◯◯◯ VERY LOW	14/2198 (0.6%)	6/1024 (0.6%)	RR 1.34 (0.57 to 3.11)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Insulin (follow-up: range 12-26 weeks)											
1029 (2 RCTs)	serious[a]	not serious	not serious	very serious[h]	none	⨁◯◯◯ VERY LOW	1/418 (0.2%)	4/611 (0.7%)	RR 2.19 (0.33 to 14.42)	0 per 100	0 fewer per 100 (from 0 fewer to 3 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **DPP4-I:** dipeptidyl peptidase-4 inhibitors; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.1.6.1 GRADE evidence

a. Eight studies that carried small weight DPP4-Is vs. AHGs (0.7%, 0.6%, 0.4%, 0.4%, 0.4%, 0.3%, 0.2%, and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (53), in which 4 studies were unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.76). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (39) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.04). However, all studies reported an overlap CIs, in which (4) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (301) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (P=0.32). However, all studies reported an overlap CIs, in which (5) studies reported wide CI. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (37) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.55). However, all studies reported an overlap CIs, in which (2) studies reported wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (10) events with small sample size.

f. The overall imprecision was precise without a significant effect difference (P=0.10). However, all studies reported an overlap CIs, in which (3) studies reported wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (10) events with small sample size.

g. The overall imprecision was precise without a significant effect difference (P=0.50). However, all studies reported an overlap CIs, in which (3) studies reported wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (20) events with large sample size.

h. The overall imprecision was precise without a significant effect difference (P=0.41). However, all studies reported an overlap CIs, in which (2) studies reported wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (5) events with small sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (P=0.17). However, the majority of studies reported an overlap CIs, in which (25) reported wide CIs. The small studies 4.7% and 0.4% did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of DPP4-Is favour across sulfonylurea and favour non-DPP4-Is (SGLT2-Is), respectively. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (422) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.93; I^2=0%) or a subgroup difference (P=0.27; I^2=21.5%). Majority of studies at low risk of bias (96.8%). No evidence of detection of bias. However, our confidence may decrease because the

magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, eight studies with open-label design out of 53. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, a study reports an outlier outside the pyramid edge due to multiple interventional groups consequently to a very wide CI.

3.7.2 GLP1-RAs class

3.7.2.1 GLP1-RAs and non-fatal stroke by subtypes

Supplemental Table 3-16. GRADE evidence profile of GLP1-RAs and non-fatal stroke by subtypes

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With GLP1-RAs		Risk with placebo / controls	Risk difference with GLP1-RAs
GLP1-RAs non-fatal stroke by subtypes and treatment allocation (follow-up: range 16-339 weeks)											
76843 (33 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	817/37487 (2.2%)	703/39356 (1.8%)	RR 0.85 (0.77 to 0.94)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Ischaemic stroke GLP1-RAs vs. placebo (follow-up: range 16-339 weeks)											
59696 (18 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ LOW	790/29289 (2.7%)	680/30407 (2.2%)	RR 0.85 (0.77 to 0.94)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Haemorrhagic stroke GLP1-RAs vs. placebo (follow-up: mean 104 weeks)											
3297 (1 RCT)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	4/1649 (0.2%)	2/1648 (0.1%)	RR 0.50 (0.09 to 2.73)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic stroke GLP1-RAs vs. AHGs (follow-up: range 26-235 weeks)											
10747 (15 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ VERY LOW	22/5085 (0.4%)	18/5662 (0.3%)	RR 0.80 (0.45 to 1.44)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic stroke GLP1-RAs vs. AHGs (follow-up: range 27-156 weeks)											
3103 (4 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	1/1464 (0.1%)	3/1639 (0.2%)	RR 1.66 (0.41 to 6.73)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RR:** Risk ratio.

3.7.2.1.1 GRADE evidence

a. Eleven studies that carried small weight GLP1-RAs vs. placebo (0.5%, 0.2%, and 0.1%), GLP1-RAs vs. AHGs (ischaemic stroke (0.3%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (33), in which one study was unpublished RCTs.

b. The overall imprecision was precise with a significant effect difference (P=0.002). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (1,470) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.42). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (6) events with large size.

d. The overall imprecision was precise without a significant effect difference (P=0.46). However, all studies reported an overlap CIs, in which (8) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (40) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.48). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for small benefit not exceeding a minimal important difference, including only (4) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with very significant effect level of evidence difference (P=0.002). However, the majority of studies reported an overlap CIs, in which (16) reported wide CIs. The large study (21.1%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of GLP1-RAs favour across placebo. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,520) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.97; I^2=0%) or a subgroup difference (P=0.73; I^2=0%). Majority of studies at low risk of bias (98.0%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 11 studies with open-label design out of 33, in which one study was unpublished RCTs. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.2.2 GLP1-RAs and fatal stroke risk

Supplemental Table 3-17. GRADE evidence profile of GLP1-RAs and fatal stroke risk

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With GLP1-RAs		Risk with placebo / controls	Risk difference with GLP1-RAs
GLP1-RAs fatal stroke (follow-up: range 16-339 weeks)											
46097 (7 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	102/22866 (0.4%)	79/23231 (0.3%)	RR 0.78 (0.58 to 1.04)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic fatal stroke GLP1-RAs vs. placebo (follow-up: range 84-339 weeks)											
43456 (4 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	100/21752 (0.5%)	78/21704 (0.4%)	RR 0.78 (0.58 to 1.05)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic fatal stroke GLP1-RAs vs. AHGs (follow-up: mean 26 weeks)											
911 (1 RCT)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ VERY LOW	1/450 (0.2%)	0/461 (0.0%)	RR 0.33 (0.01 to 7.97)	0 per 100	0 fewer per 100 (from 0 fewer to 2 more)
Haemorrhagic fatal stroke GLP1-RAs vs. AHGs (follow-up: range 26-104 weeks)											
1730 (2 RCTs)	serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ VERY LOW	1/664 (0.2%)	1/1066 (0.1%)	RR 0.70 (0.07 to 6.72)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RR:** Risk ratio.

3.7.2.2.1 GRADE evidence

a. Two studies that carried small weight GLP1-RAs vs. AHGs (ischaemic stroke (1.5%) and (haemorrhagic stroke (0.6%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (7).

b. The overall imprecision was precise without a significant effect difference (*P*=0.08). However, all studies reported a narrow CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (181) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.10). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (178) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (*P*=0.49). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (1) event with small sample size (911).

e. The overall imprecision was precise without a significant effect difference (*P*=0.73). However, all studies reported an overlap CIs, in which one study reported a wide CI. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with small sample size (1,730).

In summary, the overall certainty of the pooled EE was with very low precise imprecision without significant effect level of evidence difference (*P*=0.08). However, the majority of studies reported an overlap CIs, in which one reported a wide CI. All studies cross the line of no difference (1). The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including (181) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.92; I^2=0%) or a subgroup difference (*P*=0.86; I^2=0%). Majority of studies at low risk of bias (97.9%). No evidence of detection or selection bias. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.2.3 GLP1-RAs by baseline characteristics

Supplemental Table 3-18. GRADE evidence profile of GLP1-RAs by baseline characteristics

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With GLP1-RAs		Risk with placebo / controls	Risk difference with GLP1-RAs
Risk of stroke in T2DM by baseline characteristics (follow-up: range 16-339 weeks)											
70443 (33 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	884/34374 (2.6%)	753/36069 (2.1%)	RR 0.84 (0.77 to 0.93)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Risk of stroke in T2DM GLP1-RAs vs. placebo (follow-up: range 16-156 weeks)											
3692 (11 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ VERY LOW	10/1262 (0.8%)	14/2430 (0.6%)	RR 0.72 (0.36 to 1.42)	1 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Risk of stroke in T2DM GLP1-RAs vs. AHGs (follow-up: range 26-235 weeks)											
10747 (15 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⨁◯◯◯ VERY LOW	24/5085 (0.5%)	21/5662 (0.4%)	RR 0.85 (0.48 to 1.49)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM and CVD GLP1-RAs vs. placebo (follow-up: range 84-339 weeks)											
40184 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	591/20114 (2.9%)	506/20070 (2.5%)	RR 0.86 (0.76 to 0.96)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Risk of stroke in T2DM with CVD and CKD GLP1-RAs vs. placebo (follow-up: range 104-198 weeks)											
15820 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	259/7913 (3.3%)	212/7907 (2.7%)	RR 0.82 (0.69 to 0.98)	3 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CVD:** cardiovascular disease; **CI:** Confidence interval; **CKD:** chronic kidney disease; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RR:** Risk ratio; **T2DM:** type 2 diabetes mellitus.

3.7.2.3.1 GRADE evidence

a. Eleven studies that carried small weight GLP1-RAs vs. placebo (in T2DM (0.4%, 0.2%, and 0.1%), GLP1-RAs vs. AHGs (in T2DM (0.3%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (33), in which one study was unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.34). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (24) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.56). However, all studies reported an overlap, in which (7) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (45) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with very very significant effect level of evidence difference (P=0.0005). However, the majority of studies reported an overlap CIs, in which (13) reported wide CIs. The large (22.9%) and small study (4.9%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of GLP1-RAs favour across placebo in people with T2DM with CVD and CKD. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,637) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.91; I^2=0%) or a subgroup difference (P=0.94; I^2=0%). Majority of studies at low risk of bias (98.1%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 11 studies with open-label design out of 33, in which one study was unpublished RCTs. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.2.4 GLP1-RAs by clinical trial size

Supplemental Table 3-19. GRADE evidence profile of GLP1-RAs by clinical trial size

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With GLP1-RAs		Risk with placebo / controls	Risk difference with GLP1-RAs
Risk of stroke risk by clinical trial size (follow-up: range 16-339 weeks)											
70443 (33 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	884/34374 (2.6%)	753/36069 (2.1%)	RR 0.84 (0.77 to 0.93)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Small RCTs GLP1-RAs vs. placebo (follow-up: range 16-156 weeks)											
3692 (11 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	10/1262 (0.8%)	14/2430 (0.6%)	RR 0.72 (0.36 to 1.42)	1 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Large RCTs GLP1-RAs vs. placebo (follow-up: range 84-339 weeks)											
56004 (7 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	850/28027 (3.0%)	718/27977 (2.6%)	RR 0.85 (0.77 to 0.93)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Small RCTs GLP1-RAs vs. AHGs (follow-up: range 26-235 weeks)											
10747 (15 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	24/5085 (0.5%)	21/5662 (0.4%)	RR 0.85 (0.48 to 1.49)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RCTs:** randomise controlled trials; **RR:** Risk ratio.

3.7.2.4.1 GRADE evidence

a. Eleven small RCTs studies that carried small weight GLP1-RAs vs. placebo (0.4%, 0.2%, and 0.1%), GLP1-RAs vs. AHGs (0.3%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1% and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (33), in which one study was unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.34). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (24) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.56). However, all studies reported an overlap, in which (7) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (45) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with very very significant effect level of evidence difference (P=0.0005). However, the majority of studies reported an overlap CIs, in which (13) reported wide CIs. The large (22.9%) and small study (4.9%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of GLP1-RAs favour across placebo in large RCTs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (1,637) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.91; I^2=0%) or a subgroup difference (P=0.89; I^2=0%). Majority of studies at low risk of bias (98.1%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 11 studies with open-label design out of 33, in which one study was unpublished RCTs. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.2.5 GLP1-RAs and stroke by GLP1-RAs by treatment allocation sub-class

Supplemental Table 3-20. GRADE evidence profile of GLP1-RAs and stroke by GLP1-RAs treatment allocation sub-class stratification

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With GLP1-RAs		Risk with controls	Risk difference with GLP1-RAs
Risk of stroke in T2DM by GLP1-RAs treatment allocation sub-class (follow-up: range 16-339 weeks)											
70443 (33 studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	884/34374 (2.6%)	753/36069 (2.1%)	RR 0.84 (0.77 to 0.93)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Albiglutide vs. placebo (follow-up: range 24-156 weeks)											
10366 (4 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	115/5035 (2.3%)	100/5331 (1.9%)	RR 0.83 (0.64 to 1.09)	2 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Albiglutide vs. AHGs (follow-up: range 32-156 weeks)											
2930 (4 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	11/1449 (0.8%)	11/1481 (0.7%)	RR 1.07 (0.44 to 2.61)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Dulaglutide vs. placebo (follow-up: range 28-339 weeks)											
10901 (3 RCTs)	not serious	not serious	not serious	serious[d]	none	⊕⊕⊕◯ MODERATE	205/5243 (3.9%)	162/5658 (2.9%)	RR 0.79 (0.64 to 0.96)	4 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)
Exenatide vs. placebo (follow-up: range 16-167 weeks)											
15625 (4 RCTs)	serious[a]	not serious	not serious	serious[e]	none	⊕⊕◯◯ LOW	219/7743 (2.8%)	189/7882 (2.4%)	RR 0.86 (0.71 to 1.04)	3 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Exenatide vs. AHGs (follow-up: range 26-235 weeks)											
4156 (6 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⊕◯◯◯ VERY LOW	5/1992 (0.3%)	5/2164 (0.2%)	RR 0.93 (0.32 to 2.71)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Liraglutide vs. placebo (follow-up: range 36-198 weeks)											
9597 (2 RCTs)	not serious	not serious	not serious	serious[g]	none	⊕⊕⊕◯ MODERATE	200/4802 (4.2%)	174/4795 (3.6%)	RR 0.87 (0.71 to 1.06)	4 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)
Liraglutide vs. AHGs (follow-up: range 62-52 weeks)											
2488 (4 RCTs)	serious[a]	not serious	not serious	very serious[h]	none	⊕◯◯◯ VERY LOW	8/1259 (0.6%)	3/1229 (0.2%)	RR 0.44 (0.14 to 1.34)	1 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Lixisenatide vs. placebo (follow-up: mean 109 weeks)											
6068 (1 RCT)	not serious	not serious	not serious	very serious[i]	none	⊕⊕◯◯ LOW	60/3034 (2.0%)	67/3034 (2.2%)	RR 1.12 (0.79 to 1.58)	2 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Semaglutide vs. placebo (follow-up: mean 104 weeks)											
6480 (2 studies)	not serious	not serious	not serious	very serious[j]	none	⊕⊕◯◯ LOW	60/3241 (1.9%)	39/3239 (1.2%)	RR 0.65 (0.44 to 0.97)	2 per 100	1 fewer per 100 (from 1 fewer to 0 fewer)
Tspoglutide vs. placebo (follow-up: mean 24 weeks)											
659 (2 RCTs)	serious[a]	not serious	not serious	very serious[k]	none	⊕◯◯◯ VERY LOW	1/191 (0.5%)	1/468 (0.2%)	RR 0.40 (0.05 to 2.99)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Tspoglutide vs. AHGs (follow-up: mean 104 weeks)											
1173 (1 RCT)	serious[a]	not serious	not serious	very serious[l]	none	⊕◯◯◯ VERY LOW	0/385 (0.0%)	2/788 (0.3%)	RR 2.45 (0.12 to 50.83)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **GLP1-RAs:** glucagon-like receptor peptide-1 agonist; **RR:** Risk ratio.

3.7.2.5.1 GRADE evidence

a. Eleven studies that carried small weight GLP1-RAs vs. placebo (0.4%, 0.2%, and 0.1%) and GLP1-RAs vs. AHGs (0.3%, 0.2%, 0.2%, 0.1%, 0.1%, 0.1%, 0.1%, and 0.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (33), in which one study was unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.18). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (215) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.89). However, all studies reported an overlap CIs, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (22) events with small sample size.

d. The overall imprecision was precise with a significant effect difference (P=0.02). However, all studies reported an overlap, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (367) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.13). However, all studies reported an overlap, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (408) events with large sample size.

f. The overall imprecision was precise without a significant effect difference (P=0.89). However, all studies reported an overlap, in which (3) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (10) events with large sample size.

g. The overall imprecision was precise without a significant effect difference (P=0.17). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (374) events with small sample size.

h. The overall imprecision was precise without a significant effect difference (P=0.15). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (11) events with large sample size.

i. The overall imprecision was precise without a significant effect difference (P=0.53). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (127) events with large sample size.

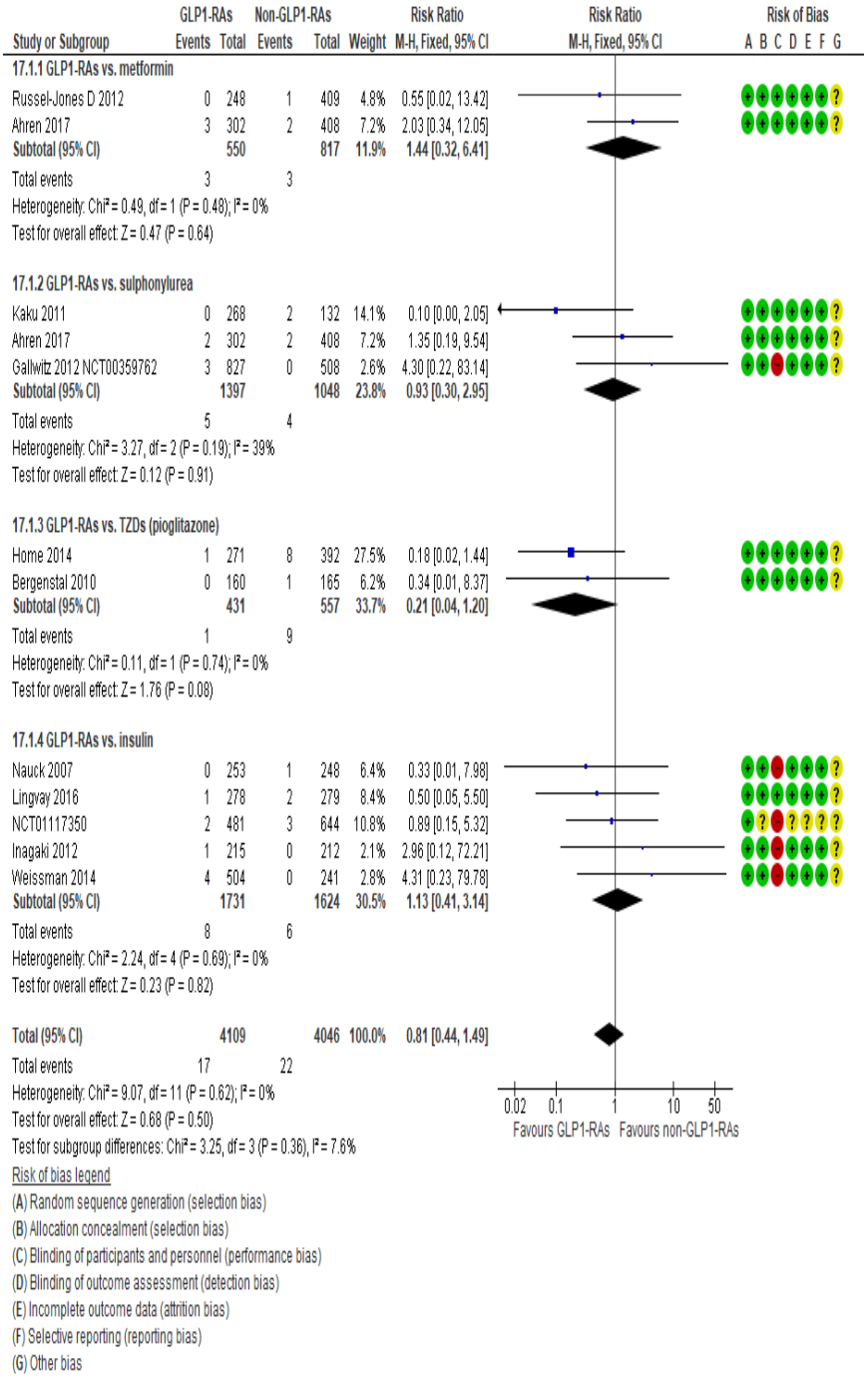
j. The overall imprecision was precise with a significant effect difference (P=0.03). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (99) events with large sample size.

k. The overall imprecision was precise without a significant effect difference (P=0.37). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with small sample size (659).

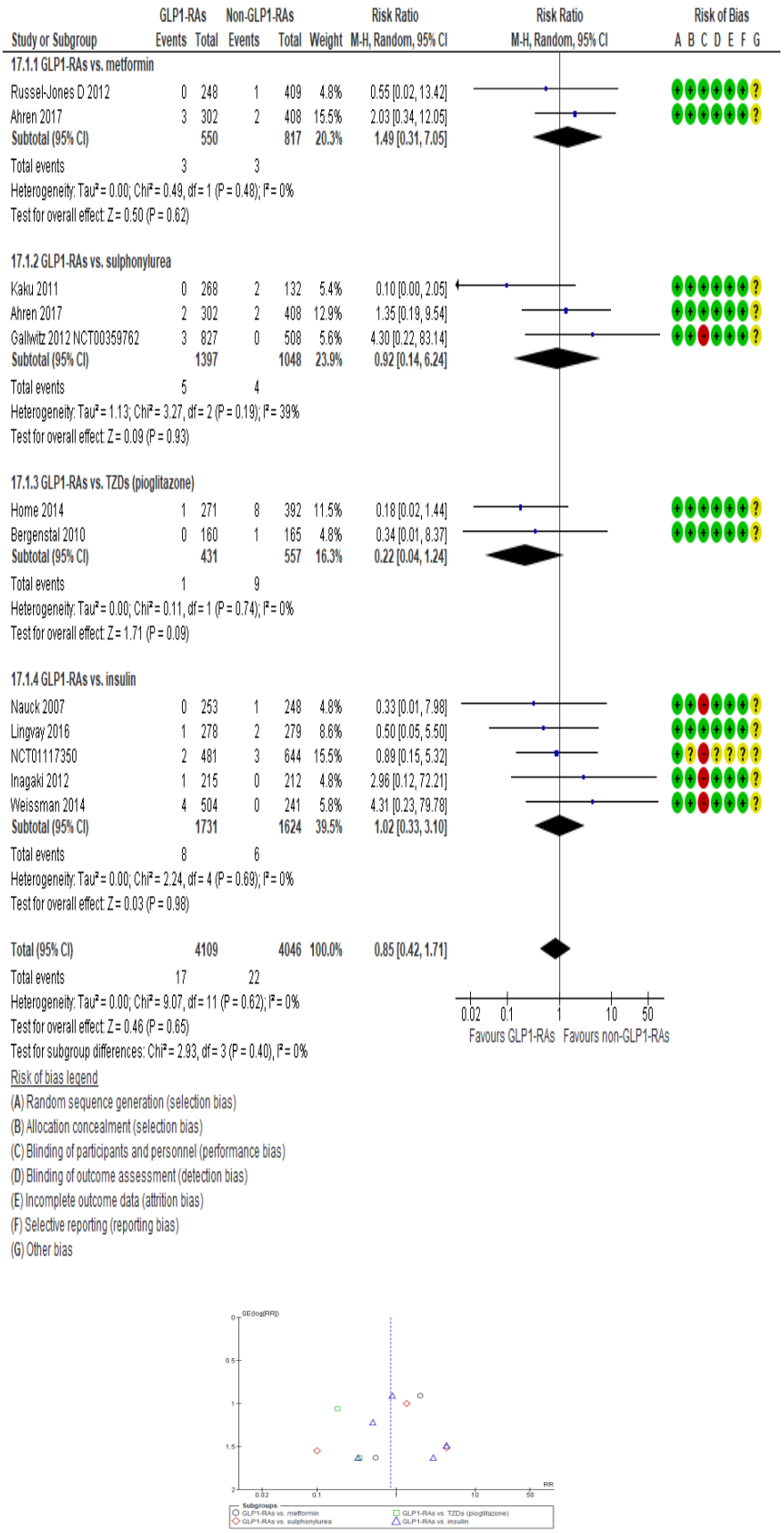
l. The overall imprecision was precise without a significant effect difference (P=0.56). However, all studies reported an overlap, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision with a very very significant effect level of evidence difference (P=0.0005). However, the majority of studies reported an overlap CIs, in which (13) reported wide CIs. The large (23.3%) and small study (5.0%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of GLP1-RAs favour across placebo. The 95% CI was consistent with the possibility for a benefit exceeding a minimal important difference, including (1,637) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.91; I^2=0%) or a subgroup difference (P=0.69; I^2=0%). Majority of studies at low risk of bias (98.1%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 11 studies with open-label design out of 33, in which one study was unpublished RCTs. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.2.6 GLP1-RAs and stroke by AHGs sub-class



Supplemental Figure 3-4. Forest and funnel plot of GLP1-RAs and stroke by AHGs sub-class, Fixed-effect model.



Supplemental Figure 3-5. Forest and funnel plot of GLP1-RAs and stroke by AHGs sub-class, Random-effect model.

Supplemental Table 3-21. GRADE evidence profile of GLP1-RAs and stroke by AHGs sub-class

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With GLP1-As		Risk with controls	Risk difference with GLP1-As
Risk of stroke in T2DM by GLP1-RAs vs. AHGs sub-class (follow-up: range 26-235 weeks)											
8155 (12 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ VERY LOW	22/4046 (0.5%)	17/4109 (0.4%)	RR 0.81 (0.44 to 1.49)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Metformin (follow-up: range 36-156 weeks)											
1367 (2 RCTs)	not serious	not serious	not serious	very serious[c]	none	⨁⨁◯◯ LOW	3/817 (0.4%)	3/550 (0.5%)	RR 1.44 (0.32 to 6.41)	0 per 100	0 fewer per 100 (from 0 fewer to 2 more)
Sulfonylurea (follow-up: range 36-235 weeks)											
2445 (3 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⨁◯◯◯ VERY LOW	4/1048 (0.4%)	5/1397 (0.4%)	RR 0.93 (0.30 to 2.95)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
TZDs pioglitazone (follow-up: mean 156 weeks)											
988 (2 RCTs)	not serious	not serious	not serious	very serious[e]	none	⨁⨁◯◯ LOW	9/557 (1.6%)	1/431 (0.2%)	RR 0.21 (0.04 to 1.20)	2 per 100	1 fewer per 100 (from 2 fewer to 0 fewer)
Insulin (follow-up: range 26-156 weeks)											
3355 (5 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⨁◯◯◯ VERY LOW	6/1624 (0.4%)	8/1731 (0.5%)	RR 1.13 (0.41 to 3.14)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **GLP1-RAs:** glucagon-like peptide-1 receptor agonist; **RR:** Risk ratio.

3.7.2.6.1 GRADE evidence

a. Five studies that carried small weight GLP1-RAs vs. AHGs (10.8%, 6.4%, 2.6%, 2.8% and 2.1%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (12), in which one study was unpublished RCTs.

b. The overall imprecision was precise without a significant effect difference (P=0.62). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (39) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.50). However, all studies reported an overlap and wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (6) events with small sample size (1,367).

d. The overall imprecision was precise without a significant effect difference (P=0.91). However, all studies reported an overlap, in which (1) study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (9) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (P=0.08). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (10) events with small sample size (988).

f. The overall imprecision was precise without a significant effect difference (P=0.82). However, all studies reported an overlap, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (14) events with large sample size.

In summary, the overall certainty of the pooled EE was with very low precise imprecision without a significant effect level of evidence difference (P=0.50). However, the majority of studies reported an overlap CIs, in which (6) reported wide CIs. All studies cross the line of no difference (1). The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including (39) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.62; I^2=0%) or a subgroup difference (P=0.36; I^2=7.6%). Majority of studies at low risk of bias (75.3%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, 5 studies with open-label design out of 12, in which one study was unpublished RCTs. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.3 SGLT-Is class

3.7.3.1 SGLT2-Is and non-fatal stroke subtypes

Supplemental Table 3-22. GRADE evidence profile of SGLT2-Is and non-fatal stroke subtypes

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With SGLT2-Is		Risk with placebo / controls	Risk difference with SGLT2-Is
SGLT2-Is non-fatal stroke by subtypes and treatment allocation (follow-up: range 12-318 weeks)											
59869 (46 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	349/22607 (1.5%)	477/37262 (1.3%)	RR 1.01 (0.88 to 1.15)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic stroke SGLT2-Is vs. placebo (follow-up: range 12-318 weeks)											
42332 (33 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ LOW	321/16749 (1.9%)	434/25583 (1.7%)	RR 1.03 (0.89 to 1.19)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic stroke SGLT2-Is vs. placebo (follow-up: range 24-318 weeks)											
1801 (4 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	3/602 (0.5%)	3/1199 (0.3%)	RR 0.50 (0.14 to 1.85)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ischaemic stroke SGLT2-Is vs. AHGs (follow-up: range 12-156 weeks)											
12067 (14 RCTs)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ VERY LOW	22/3866 (0.6%)	38/8201 (0.5%)	RR 0.94 (0.58 to 1.52)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Haemorrhagic stroke SGLT2-Is vs. AHGs (follow-up: range 52-104 weeks)											
3669 (3 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	3/1390 (0.2%)	2/2279 (0.1%)	RR 0.42 (0.08 to 2.12)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.3.1.1 GRADE evidence

a. Five studies that carried small weight SGLT2-Is vs. placebo (ischaemic stroke (0.3%, 0.2% and 0.2%) and vs. SGLT2-Is AHGs (ischaemic stroke (1.3% and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (46).

b. The overall imprecision was precise without a significant effect difference (*P*=0.68). However, all studies reported an overlap CIs, in which (13) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit exceeding a minimal important difference, including only (755) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.19). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (5) events with small sample size (1,801).

d. The overall imprecision was precise without a significant effect difference (*P*=0.79). However, all studies reported an overlap CIs, in which (8) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (60) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (*P*=0.29). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (5) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (*P*=0.93). However, the majority of studies reported an overlap CIs, in which (24) reported wide CIs. The small study (1.3%) did not cross the line of no difference (1), in which reports a significant reduction of ischaemic stroke in the direction of SGLT2-Is favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (825) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.95; I^2=0%) or a subgroup difference (*P*=0.38; I^2=2.1%). Majority of studies at low risk of bias (97.8%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, five studies with open-label design out of 46. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, one study reports an outlier outside the pyramid edge due to multiple interventional groups consequently to a very wide CI.

3.7.3.2 SGLT2-Is and fatal stroke risk

Supplemental Table 3-23. GRADE evidence profile of SGLT2-Is and fatal stroke risk

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With SGLT2-Is		Risk with placebo	Risk difference with SGLT2-Is
SGLT2-Is fatal stroke vs. placebo (follow-up: range 24-219 weeks)											
8538 (3 RCTs)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ LOW	10/2941 (0.3%)	15/5597 (0.3%)	RR 0.74 (0.34 to 1.61)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.3.2.1 GRADE evidence

a. The overall imprecision was precise without a significant effect difference (*P*=0.45). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (25) events with large sample size.

In summary, the overall certainty of the pooled EE was with low precise imprecision without significant effect level of evidence difference (*P*=0.45). However, the majority of studies reported an overlap CIs, in which one reported wide CIs. All studies cross the line of no difference (1). The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including (25) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.87; I^2=0%). All studies at low risk of bias (100%). No evidence of detection or selection bias. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

3.7.3.3 SGLT2-Is by baseline characteristics

Supplemental Table 3-24. GRADE evidence profile of SGLT2-Is by baseline characteristics

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With SGLT2-Is		Risk with placebo / controls	Risk difference with SGLT2-Is
Risk of stroke in T2DM by baseline characteristics (follow-up: range 12-318 weeks)											
2949 (46 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	355/20133 (1.8%)	491/32816 (1.5%)	RR 1.01 (0.89 to 1.16)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM SGLT2-Is vs. placebo (follow-up: range 12-104 weeks)											
11983 (23 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	19/3466 (0.5%)	29/8517 (0.3%)	RR 0.63 (0.38 to 1.03)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM SGLT2-Is vs. AHGs (follow-up: range 12-156 weeks)											
12067 (14 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	25/3866 (0.6%)	48/8201 (0.6%)	RR 1.01 (0.64 to 1.59)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Risk of stroke in T2DM and CVD SGLT2-Is vs. placebo (follow-up: range 52-318 weeks)											
2349 (3 RCTs)	not serious	not serious	not serious	very serious[d]	none	⊕⊕◯◯ LOW	6/1098 (0.5%)	5/1251 (0.4%)	RR 0.70 (0.21 to 2.32)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Risk of stroke in T2DM and CKD SGLT2-Is vs. placebo (follow-up: range 12-219 weeks)											
26550 (6 RCTs)	not serious	not serious	not serious	serious[e]	none	⊕⊕⊕◯ MODERATE	305/11703 (2.6%)	409/14847 (2.8%)	RR 1.06 (0.92 to 1.23)	3 per 100	0 fewer per 100 (from 0 fewer to 1 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CVD:** cardiovascular disease; **CI:** Confidence interval; **CKD:** chronic kidney disease; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors; **T2DM:** type 2 diabetes mellitus.

3.7.3.3.1 GRADE evidence

a. Five studies in people with T2DM that carried small weight SGLT2-Is vs. placebo (0.3%, 0.2% and 0.2%) and vs. SGLT2-Is AHGs (ischaemic stroke (1.3% and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (46).

b. The overall imprecision was precise without a significant effect difference (*P*=0.06). However, all studies reported an overlap CIs, in which (11) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (48) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.96). However, all studies reported an overlap CIs, in which (8) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (73) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (*P*=0.56). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (11) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (*P*=0.42). However, all studies reported an overlap CIs, in which a study reported wide CIs. The 95% CI was consistent with the possibility for a benefit exceeding a minimal important difference, including only (714) events with large sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (*P*=0.84). However, the majority of studies reported an overlap CIs, in which (21) reported wide CIs. The small study (1.3%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of SGLT2-Is favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (846) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.88; I^2=0%) or a subgroup difference (*P*=0.22; I^2=31.4%). Majority of studies at low risk of bias (97.8%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, five studies with open-label design out of 46. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, a study reports an outlier outside the pyramid edge due to multiple interventional groups consequently to a very wide CI.

3.7.3.4 SGLT2-Is by clinical trial size

Supplemental Table 3-25. GRADE evidence profile of SGLT2-Is by clinical trial size

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo / controls	With SGLT2-Is		Risk with placebo / controls	Risk difference with SGLT2-Is
Risk of stroke risk by clinical trial size (follow-up: range 12-318 weeks)											
52949 (46 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	355/20133 (1.8%)	491/32816 (1.5%)	RR 1.01 (0.89 to 1.16)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Small RCTs SGLT2-Is vs. placebo (follow-up: range 12-318 weeks)											
16702 (30 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⊕◯◯◯ VERY LOW	30/5356 (0.6%)	44/11346 (0.4%)	RR 0.69 (0.46 to 1.05)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Large RCTs SGLT2-Is vs. placebo (follow-up: range 161-219 weeks)											
24180 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	300/10911 (2.7%)	399/13269 (3.0%)	RR 1.06 (0.92 to 1.24)	3 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Small RCTs SGLT2-Is vs. AHGs (follow-up: range 12-156 weeks)											
12067 (14 RCTs)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ VERY LOW	25/3866 (0.6%)	48/8201 (0.6%)	RR 1.01 (0.64 to 1.59)	1 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **RCTs:** randomise controlled trials; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.3.4.1 GRADE evidence

a. Five studies that carried small weight SGLT2-Is vs. placebo (0.3%, 0.2% and 0.2%) and vs. SGLT2-Is AHGs (1.3% and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (46).

b. The overall imprecision was precise without a significant effect difference (P=0.08). However, all studies reported an overlap CIs, in which (13) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (74) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (P=0.96). However, all studies reported an overlap CIs, in which (8) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (73) events with small sample size.

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (P=0.84). However, the majority of studies reported an overlap CIs, in which (21) reported wide CIs. The small study (1.3%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of SGLT2-Is favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (846) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.88; I^2=0%) or a subgroup difference (P=0.16; I^2=45.9%). Majority of studies at low risk of bias (97.8%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, five studies with open-label design out of 46. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, one study reports an outlier outside the pyramid edge due to multiple interventional groups consequently to a very wide CI.

3.7.3.5 SGLT2-Is and stroke by SGLT2-1s by treatment allocation sub-class

Supplemental Table 3-26. GRADE evidence profile of SGLT2-Is and stroke by SGLT2-Is treatment allocation sub-class stratification

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With SGLT2-Is		Risk with controls	Risk difference with SGLT2-Is
Risk of stroke in T2DM by SGLT2-Is treatment allocation sub-class (follow-up: range 12-318 weeks)											
52949 (46 RCTs)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	354/20133 (1.8%)	489/32816 (1.5%)	RR 1.01 (0.89 to 1.16)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Canagliflozin vs. placebo (follow-up: range 18-104 weeks)											
2693 (6 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ LOW	5/864 (0.6%)	10/1829 (0.5%)	RR 0.82 (0.31 to 2.19)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Canagliflozin vs. AHGs (follow-up: range 12-52 weeks)											
5017 (5 RCTs)	not serious	not serious	not serious	very serious[c]	none	⊕⊕◯◯ LOW	5/1761 (0.2%)	17/3256 (0.5%)	RR 1.83 (0.71 to 4.71)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Dapagliflozin vs. placebo (follow-up: range 12-104 weeks)											
24172 (14 RCTs)	not serious	not serious	not serious	serious[d]	none	⊕⊕⊕◯ MODERATE	246/11117 (2.2%)	249/13055 (1.9%)	RR 0.98 (0.82 to 1.16)	2 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Dapagliflozin vs. AHGs (follow-up: range 24-156 weeks)											
1348 (2 RCTs)	not serious	not serious	not serious	very serious[e]	none	⊕⊕◯◯ LOW	1/584 (0.2%)	2/764 (0.3%)	RR 1.13 (0.23 to 5.62)	0 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Empagliflozin vs. placebo (follow-up: range 12-161 weeks)											
13555 (11 RCTs)	serious[a]	not serious	not serious	very serious[f]	none	⊕◯◯◯ VERY LOW	78/4133 (1.9%)	182/9422 (1.9%)	RR 1.13 (0.88 to 1.47)	2 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Empagliflozin vs. AHGs (follow-up: range 26-104 weeks)											
5411 (6 RCTs)	serious[a]	not serious	not serious	very serious[g]	none	⊕◯◯◯ VERY LOW	20/1424 (1.4%)	28/3987 (0.7%)	RR 0.74 (0.42 to 1.31)	1 per 100	0 fewer per 100 (from 1 fewer to 0 fewer)
Ertugliflozin vs. placebo (follow-up: mean 318 weeks)											
462 (1 RCT)	not serious	not serious	not serious	very serious[h]	none	⊕⊕◯◯ LOW	0/153 (0.0%)	2/309 (0.6%)	RR 2.48 (0.12 to 51.42)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Ertugliflozin vs. AHGs (follow-up: mean 26 weeks)											
291 (1 RCT)	not serious	not serious	not serious	very serious[i]	none	⊕⊕◯◯ LOW	1/97 (1.0%)	0/194 (0.0%)	RR 0.17 (0.01 to 4.07)	1 per 100	1 fewer per 100 (from 1 fewer to 3 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.3.5.1 GRADE evidence

a. Five studies that carried small weight SGLT2-Is empagliflozin vs. placebo (0.3%, 0.2% and 0.2%) and empagliflozin vs. AHGs (1.3% and 0.2%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (46).

b. The overall imprecision was precise without a significant effect difference (*P*=0.69). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (15) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.30). However, all studies reported an overlap CIs, in which (4) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (22) events with large sample size.

d. The overall imprecision was precise without a significant effect difference (*P*=0.74). However, all studies reported an overlap CIs, in which (6) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit exceeding a minimal important difference, including only (482) events with large sample size.

e. The overall imprecision was precise without a significant effect difference (*P*=0.88). However, all studies reported an overlap CIs, in which one study reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (3) events with small sample size (1,348).

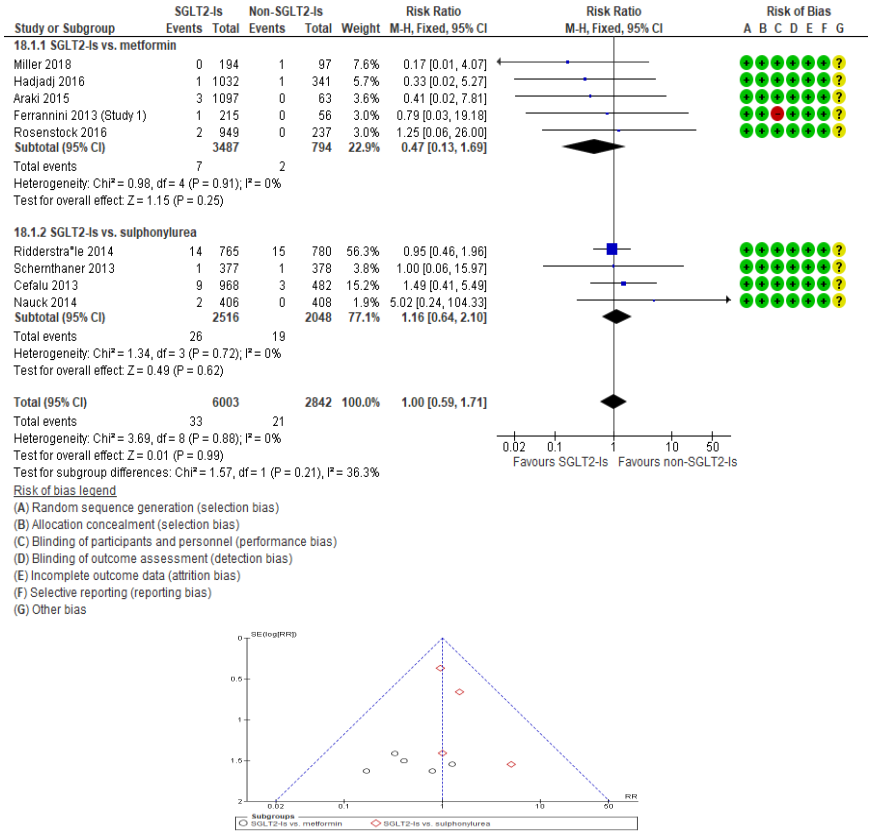
f. The overall imprecision was precise without a significant effect difference (*P*=0.34). However, all studies reported an overlap CIs, in which (4) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (260) events with large sample size.

g. The overall imprecision was precise without a significant effect difference (*P*=0.33). However, all studies reported an overlap CIs, in which two studies reported wide CIs. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including only (48) events with large sample size.

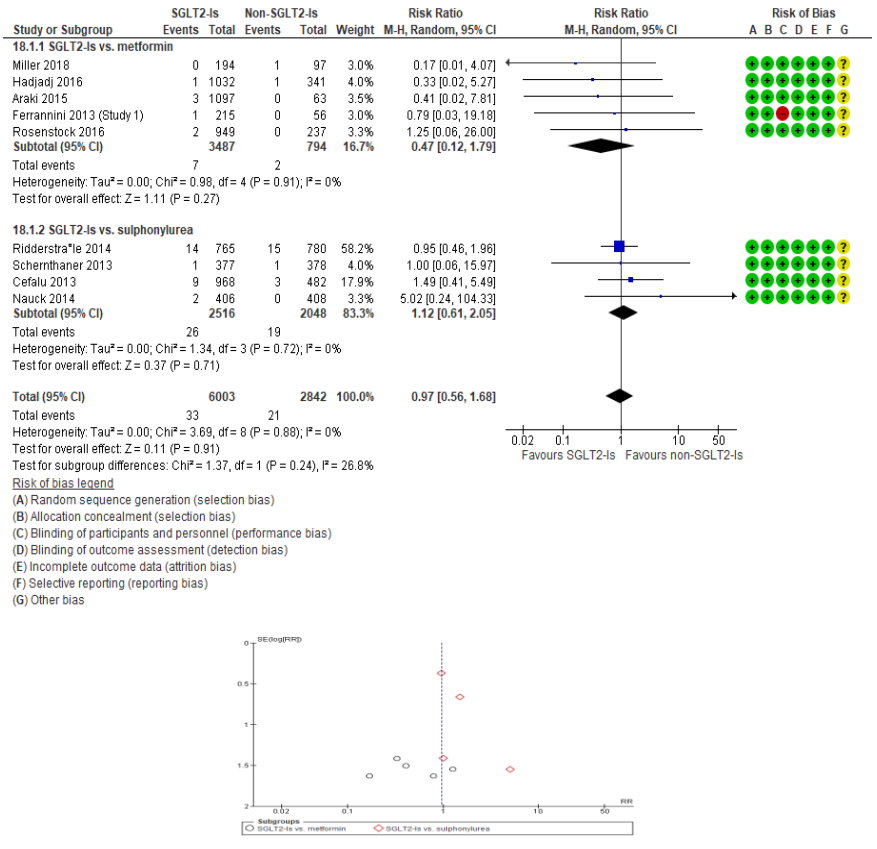
h. The overall imprecision was precise without a significant effect difference (P=0.56). However, all studies reported an overlap and wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (2) events with small sample size (462).
i. The overall imprecision was precise without a significant effect difference (P=0.27). However, all studies reported an overlap and narrow CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (1) event with small sample size (291).

In summary, the overall certainty of the pooled EE was with moderate precise imprecision without significant effect level of evidence difference (P=0.89). However, the majority of studies reported an overlap CIs, in which (20) reported wide CIs. The small study (1.3%) did not cross the line of no difference (1), in which reports a significant reduction of stroke in the direction of SGLT2-Is empagliflozin favour across active comparators. The 95% CI was consistent with the possibility for large benefit exceeding a minimal important difference, including (846) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (P=0.89; I^2=0%) or a subgroup difference (P=0.69; I^2=0%). Majority of studies at low risk of bias (97.8%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, five studies with open-label design out of 46. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias. However, a study reports an outlier outside the pyramid edge due to multiple interventional groups consequently to a very wide CI.

3.7.3.6 SGLT2-Is and stroke by AHGs sub-class



Supplemental Figure 3-6. Forest and funnel plot of SGLT2-Is and stroke by AHGs sub-class, Fixed-effect model.



Supplemental Figure 3-7. Forest and funnel plot of SGLT2-Is and stroke by AHGs sub-class, Fixed-effect model.

Supplemental Table 3-27. GRADE evidence profile of SGLT2-Is and stroke by AHGs sub-class

Certainty assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With SGLT2-Is		Risk with controls	Risk difference with SGLT2-Is
Risk of stroke in T2DM by SGLT2-Is vs. AHGs sub-class (follow-up: range 12-156 weeks)											
8845 (9 RCTs)	serious	not serious	not serious	very serious	none	⊕◯◯◯ VERY LOW	21/2842 (0.7%)	33/6003 (0.5%)	RR 1.00 (0.59 to 1.71)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)
Metformin (follow-up: range 12-78 weeks)											
4281 (5 RCTs)	serious	not serious	not serious	very serious	none	⊕◯◯◯ VERY LOW	2/794 (0.3%)	7/3487 (0.2%)	RR 0.47 (0.13 to 1.69)	0 per 100	0 fewer per 100 (from 0 fewer to 0 fewer)
Sulfonylurea (follow-up: range 52-156 weeks)											
4564 (4 RCTs)	not serious	not serious	not serious	very serious	none	⊕⊕◯◯ LOW	19/2048 (0.9%)	26/2516 (1.0%)	RR 1.16 (0.64 to 2.10)	1 per 100	0 fewer per 100 (from 0 fewer to 1 more)

Abbreviations: **AHGs:** anti-hyperglycaemic agents; **CI:** Confidence interval; **RR:** Risk ratio; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors.

3.7.3.6.1 GRADE evidence

a. A study that carried small weight SGLT2-Is empagliflozin vs. metformin (3.0%) for the overall EE rated as high risk of bias due to lack of blinding as an open-label design out of (9).

b. The overall imprecision was precise without a significant effect difference (*P*=0.25). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (9) events with large sample size.

c. The overall imprecision was precise without a significant effect difference (*P*=0.62). However, all studies reported an overlap CIs, in which (2) studies reported wide CIs. The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including only (44) events with large sample size.

In summary, the overall certainty of the pooled EE was with very low precise imprecision without significant effect level of evidence difference (*P*=0.99). However, the majority of studies reported an overlap CIs, in which (4) reported wide CIs. All studies cross the line of no difference (1). The 95% CI was consistent with the possibility for a benefit not exceeding a minimal important difference, including (54) events in total with large sample size. No evidence of inconsistency or a statistical important heterogeneity (*P*=0.88; I^2=0%) or a subgroup difference (*P*=0.21; I^2=36.3%). Majority of studies at low risk of bias (97.0%). No evidence of detection bias. However, our confidence may decrease because the magnitude impacts of some studies, that suffer from limitations, were likely to result in a biased assessment of the intervention effect consequently due to performance and selection bias, five studies with open-label design out of nine. The studies indirectness was high level of evidence with an individual study PICOS element align closely to the review PICOS. Finally, no evidence of reporting bias.

Chapter 4 Pioglitazone Use After Stroke. Exploring Stroke Survivors' Views – The PIOSurvey

4.1 Participants invitation letter

Take part in a Research Study

Dear

You very kindly joined SHARE, the Scottish Health Research Register for people interested in hearing about opportunities to help with medical research. We are writing to let you know about a research opportunity that has arisen and that might appeal to you. Please see letter from the study team below:

Study Title: "Pioglitazone use after stroke. Exploring stroke survivors' views"

This research study is being conducted by a team of researchers at the University of Glasgow.

This is an invitation to complete a survey that aims to understand your views about taking a drug called pioglitazone to reduce the risk of stroke and heart.

We feel that this is an important study and hope that you are interested in participating in this research. However, **we have not passed on your personal details and you do not have to take part**. Deciding not to participate would, in no way, affect the care you receive from the NHS.

To find out more about taking part in the questionnaire, please read the information sheet by clicking on the link below or contact the research team directly on the numbers below.

The survey will take approximately 10-15 minutes to complete. Five-hundred people will be contacted and we hope to receive over 100 responses.

If you are happy to complete the survey, you can access it and the information sheet by clicking on this link or by copying the link into your web browser.

Yours sincerely,

Professor Jesse Dawson
Professor of Stroke Medicine, University of Glasgow
jesse.dawson@glasgow.ac.uk
Tel 0141 2011100

Supplemental Figure 4-1. Participants invitation letter.

4.2 Participant information sheet

Pioglitazone use after stroke. Exploring stroke survivors' views

Introduction

We need better treatments to prevent stroke. After a stroke or a mini stroke (called a TIA) doctors prescribe a variety of medicines to reduce the risk of a second stroke. These medicines might include blood-thinning drugs, drugs to lower cholesterol and drugs to lower blood pressure. Recently we learned that a drug called pioglitazone may also prevent strokes and heart attacks in some people who have survived stroke. In this study we want to explore stroke survivors' views of Pioglitazone.

What is Pioglitazone?

Pioglitazone is a drug already used to treat diabetes. It works by making the body more sensitive to the hormone insulin, which helps control blood sugar. In diabetes, it reduces blood sugar levels and seems to have other important benefits on blood vessels and liver cells.

What might Pioglitazone help after stroke?

A recent study showed that pioglitazone reduces the risk of second stroke or heart attack in people with stroke who have insulin resistance. Insulin resistance is when someone is less responsive to the hormone insulin than normal but does not have diabetes. This might affect as many as a one-third of people with stroke. Pioglitazone removed roughly one-fourth of the risk of a stroke or heart attack. It led to three fewer people per 100 having a stroke or heart attack compared to placebo. Interestingly, about half as many patients treated with pioglitazone went on to develop diabetes in this study.

Are there any downsides to using Pioglitazone?

Yes there are, and this is why we are not currently using the drug routinely after stroke. We need to know more before we do. Pioglitazone causes side effects. Most notably, there is an increased risk of bone fracture, weight gain and ankle swelling. Pioglitazone led to two more fractures per 100 people treated. An extra six people per 100 treated gained over 13 kg (2 stones) of weight and an extra 10 people per 100 treated had ankle swelling. The mechanism through which pioglitazone increases weight gain is likely due to increased fat in peripheral tissues and retention of fluid. The increased fracture risk may be due to a reduction in the thickness of bones.

Low blood sugar (hypoglycaemia) is NOT a risk with pioglitazone. When people with normal blood sugar levels take this medicine, there is little change in their blood sugar. Also, there is unlikely to be any interaction between pioglitazone and other drugs routinely used after stroke.

What do we want to find out?

We want to understand what stroke survivors think about these risks and benefits and the use of pioglitazone after stroke. It is possible we could reduce some of the side effects and we want your thoughts on how we might do this.

Why are we writing to you?

We are asking you to help us because you have registered with SHARE. This letter does not mean that pioglitazone might benefit you. Most people with stroke do not have insulin resistance. We are writing to 500 people who may be suitable for this research and aim to have responses from at least 100 people.

How can I help?

We invite you to fill out a questionnaire. We are writing to you because you may be suitable for this research survey. If you have never suffered a stroke or mini stroke you do not need to fill this out. Also, please insure the questionnaire is only completed by the person to whom it was addressed. You can complete it on paper (enclosed), on-line (Click here), or via telephone (by calling 0141 4515871) and it should take no more than 10-15 minutes. On-line completion is our preferred method. You can request for a further paper copy by calling 0141 4515871 or via email h.azhari.1@research.gla.ac.uk

The results are anonymous meaning we will be unable to trace you. We will report the summary results of this survey at medical conferences and in a medical journal. We will not report any individual responses so you will not be identified by your responses.

The results will be collated by the research team at the University of Glasgow. By returning this questionnaire to us, you give permission for us to use the anonymised data. If you have any questions, you can contact us on h.azhari.1@research.gla.ac.uk.

What if I have questions about Pioglitazone use?

Pioglitazone is not currently a recommended treatment for stroke survivors in the UK, so you are not missing out on any recommended treatment. If you have any additional questions, you can contact the study team or your G.P.

Who is leading the study?

The study is being led by researchers and stroke doctors at the University of Glasgow. The principal investigator is Prof Jesse Dawson.

Thanks for reading this.

Supplemental Figure 4-2. Participant information sheet.

4.3 Pioglitazone uses after stroke. The PIOSurvey

Online surveys

Pioglitazone use after stroke. Exploring stroke survivors' views

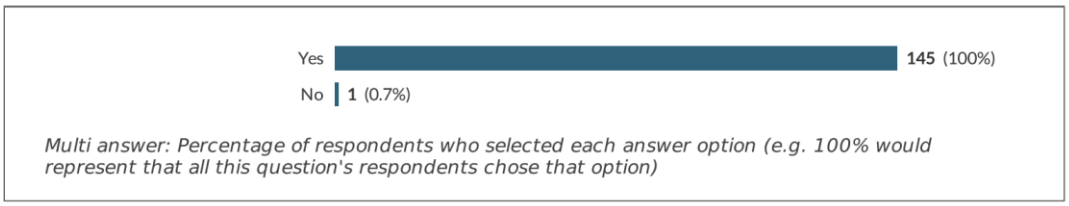
Showing 145 of 145 responses

With **9 responses excluded and 1 response deleted**

Showing **all** questions

Response rate: 28%

1 Have you read the information sheet for this study (Pioglitazone use after stroke. Exploring stroke survivors' views).

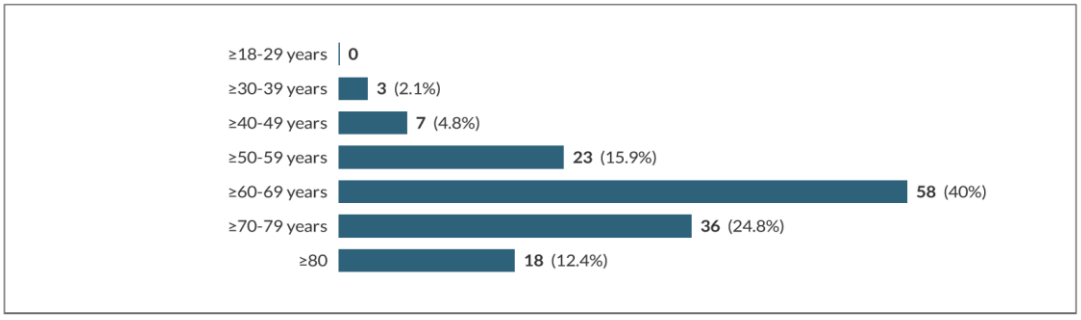


Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

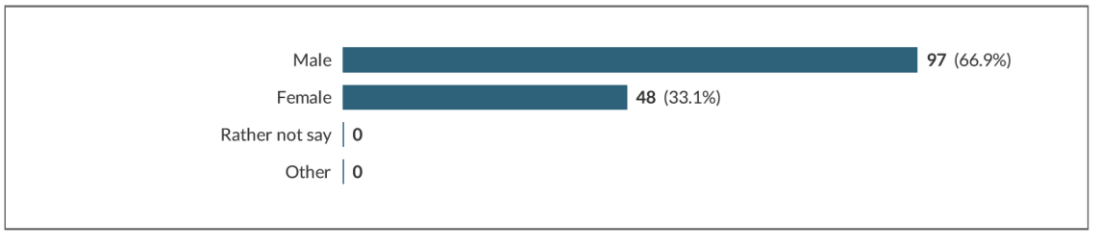
1.a If yes, do you agree to take part in the survey and for us to use your anonymous answers?

1.a.i Please confirm that this questionnaire is being completed by the person to whom it was sent.

2 What is your age?



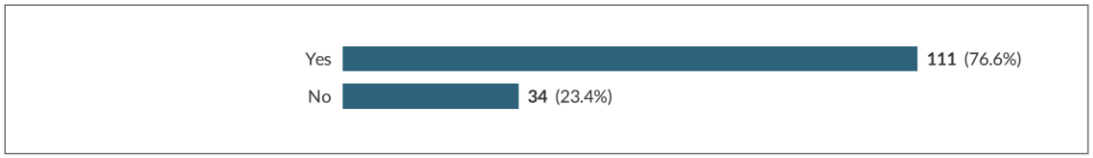
3 What is your sex?



3.a If you selected Other, please specify:

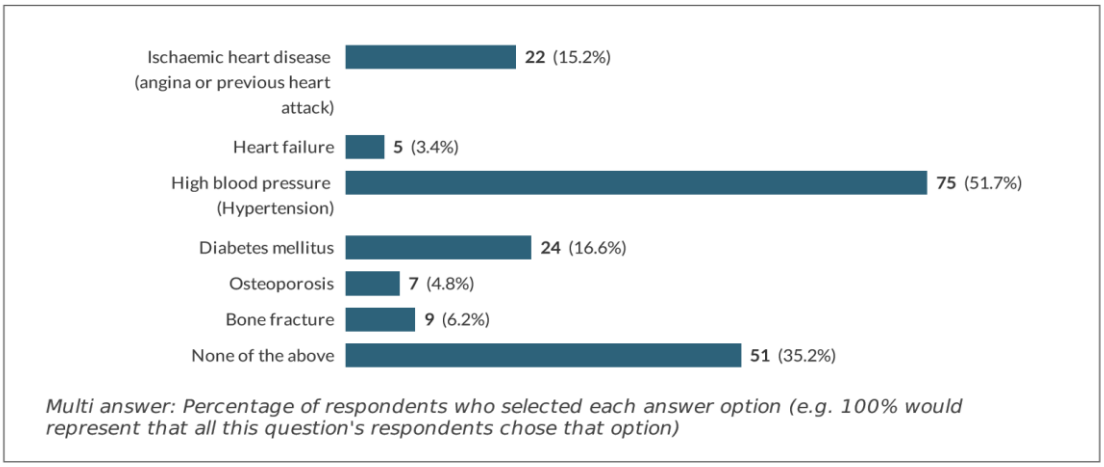
No responses

4 Has a doctor ever told you that you have had a stroke?



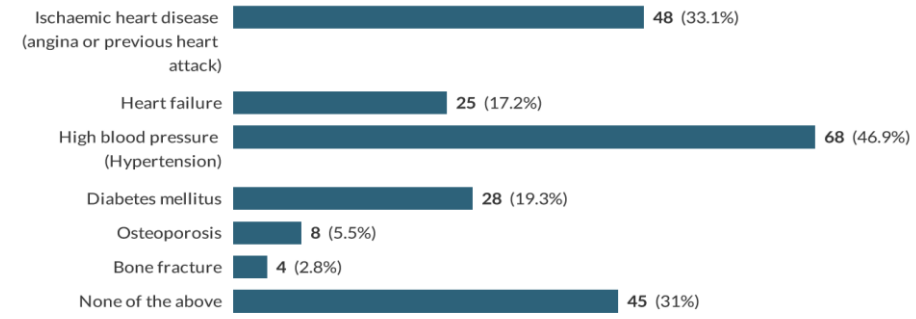
5 Has a doctor ever told you that you have had a mini-stroke or a transient ischaemic attack (TIA)?

6 Do you have any of the following health conditions? Please select ALL that apply to you.



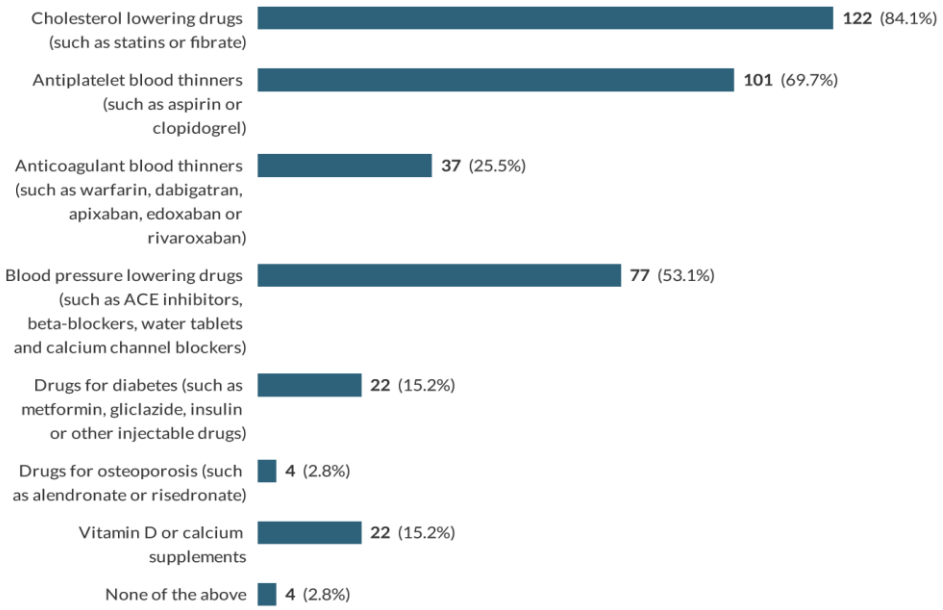
Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

7 Do you have any of the following health conditions in your family? Please select ALL that apply to you.



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

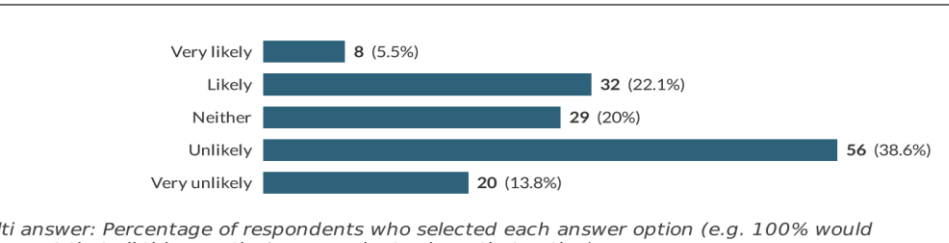
8 Do you take any of the following medications? Please select ALL that apply to you.



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

9 After reading the information about the benefits of pioglitazone, how likely are you to want to take it?

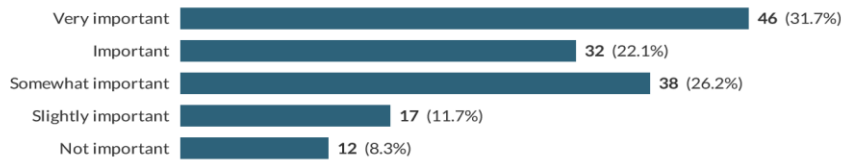
9.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

10 How important to you is the reduction in second stroke or heart attack seen with pioglitazone use?

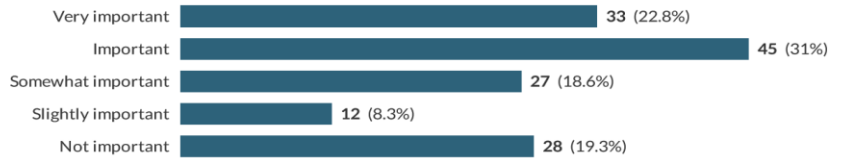
10.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

11 How important to you is the reduction in the development of diabetes seen with pioglitazone use?

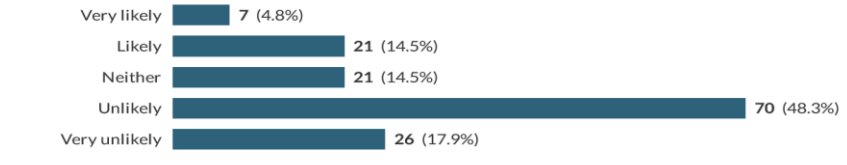
11.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

12 After reading the information about the side effects of pioglitazone, how likely are you to want to take it?

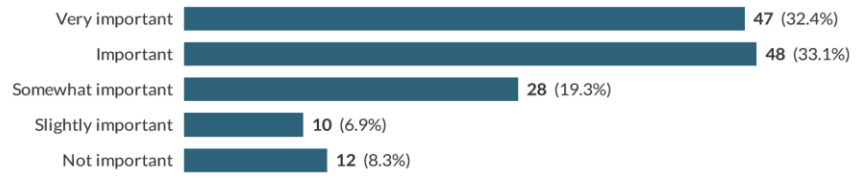
12.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

13 How important to you is the increased risk of bone fracture seen with pioglitazone use?

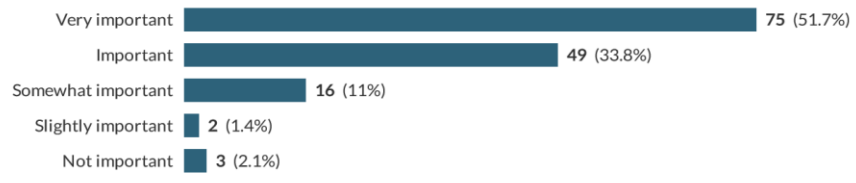
13.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

14 How important to you is the increased risk weight gain seen with pioglitazone use?

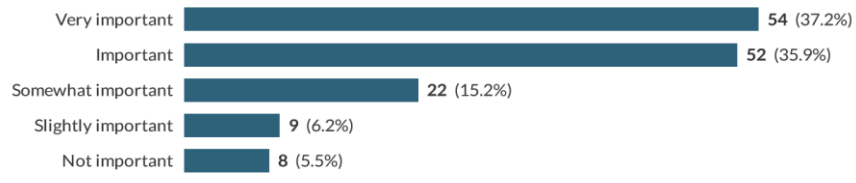
14.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

15 How important to you is the increase in ankle swelling seen with pioglitazone use?

15.1 Please check 1 box

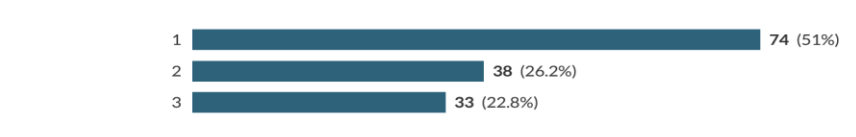


Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

16 Please rank these three side effects in order of importance to you (with 1 being the most important and 3 being the least important)

16.1 Increased risk of bone fracture

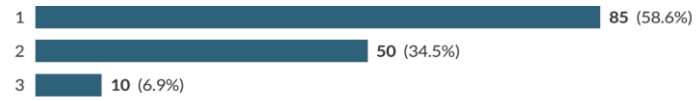
16.1.a Increased risk of bone fracture



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

16.2 Increased risk of weight gain

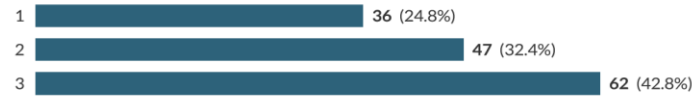
16.2.a Increased risk of weight gain



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

16.3 Increased risk of ankle swelling

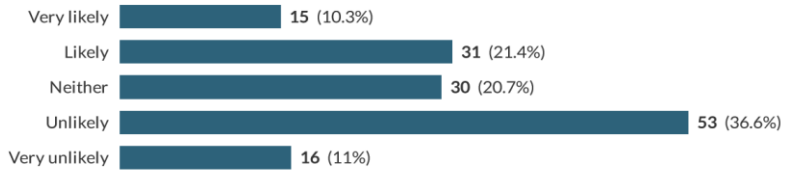
16.3.a Increased risk of ankle swelling



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

17 How likely would you be to take pioglitazone if there was no increased risk of fracture? Assume the risks of weight gain and ankle swelling remain the same.

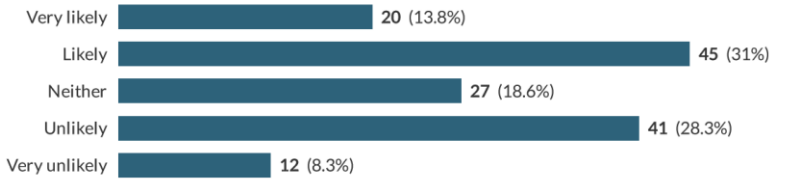
17.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

18 How likely would you be to take pioglitazone if there was no risk of weight gain? Assume the risks of fracture and ankle swelling remain the same.

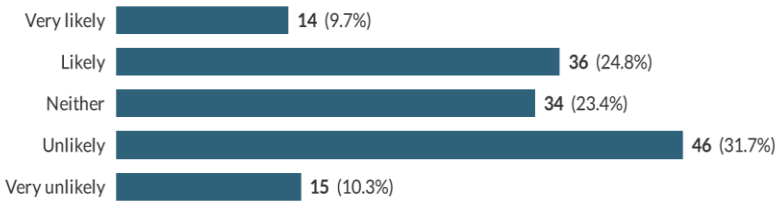
18.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

19 How likely would you be to take pioglitazone if there was no risk of ankle swelling? Assume the risks of fracture and weight gain remain the same.

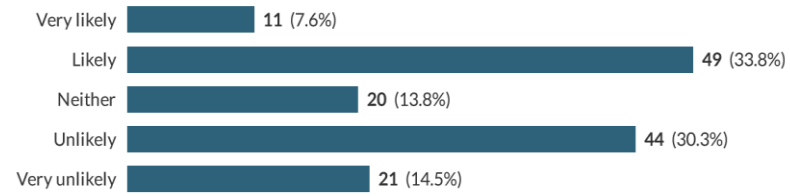
19.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

20 Would you be willing to take additional tablets to prevent risk of fracture along with pioglitazone?

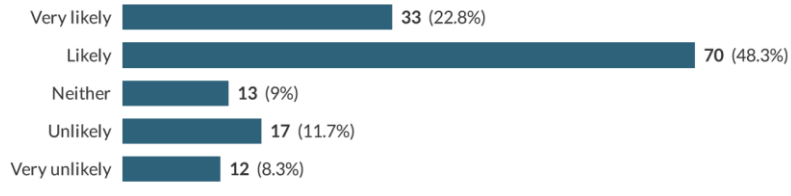
20.1 Please check 1 box



Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

21 Would you be willing to implement lifestyle changes to prevent risk of weight gain along with pioglitazone? (by this we mean to be on a controlled diet and exercise)

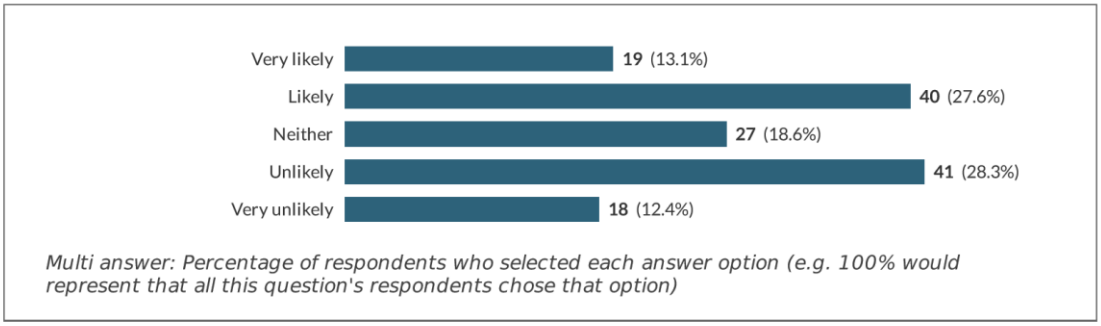
21.1 Please check 1 box



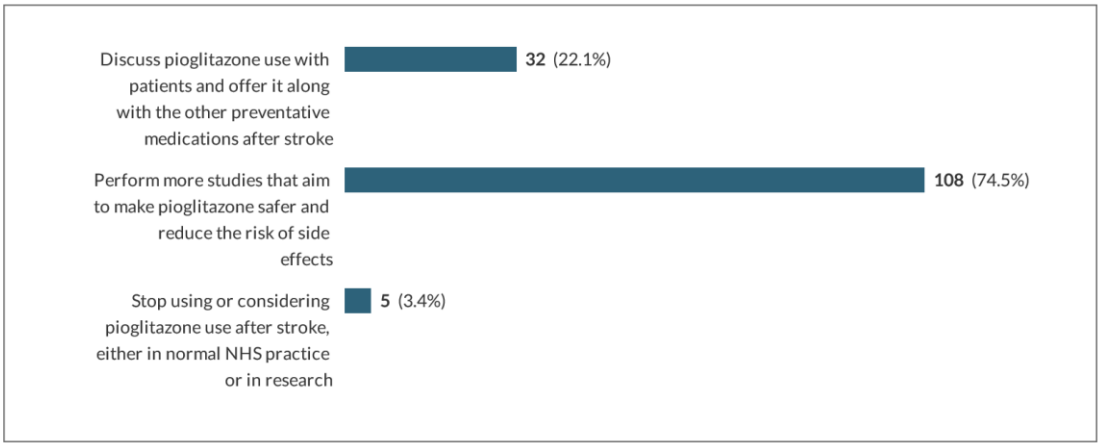
Multi answer: Percentage of respondents who selected each answer option (e.g. 100% would represent that all this question's respondents chose that option)

22 How likely would you be to take part in clinical trial seeking to make pioglitazone safer for stroke patients? (by this we mean a clinical trial that tried to reduce the side effects such as bone fracture, weight gain and ankle swelling)

22.1 Please check 1 box



23 What do you think we should do next regarding pioglitazone use after stroke? Please pick one answer that best reflects your opinion.

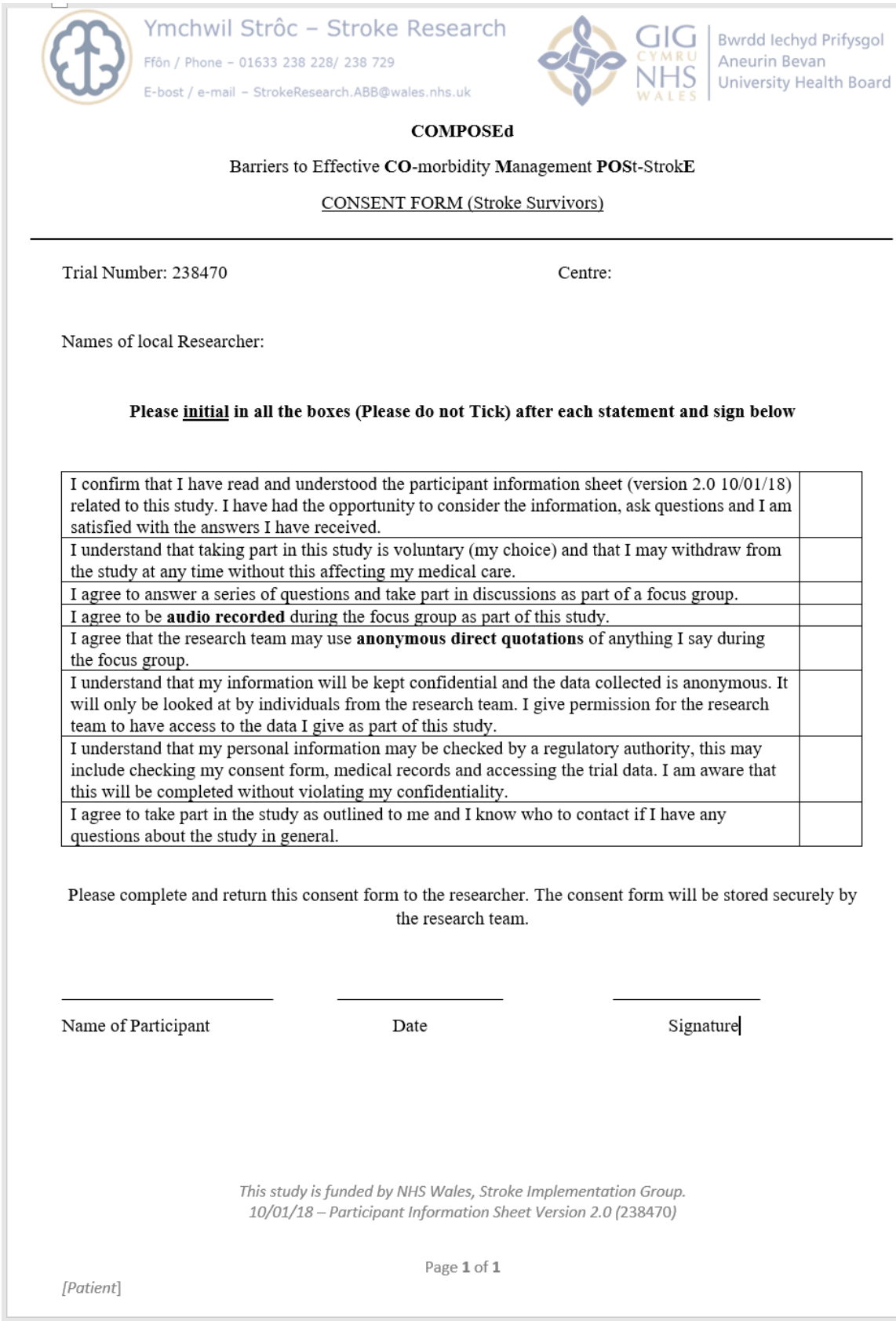


Supplemental Figure 4-3. Stroke survivors' views on pioglitazone uses after stroke. The PIOSurvey.

Chapter 5 Exploring the Barriers to Effective CO-morbidity Management POSt-StrokE with a Focus on Diabetes – The COMPOSEd study. Patients and Clinicians' Views: A Qualitative Focus Groups and Interviews Study

5.1 Participants consent form and invitation letter

5.1.1 Stroke survivors



Ymchwil Strôc – Stroke Research
Ffôn / Phone – 01633 238 228/ 238 729
E-bost / e-mail – StrokeResearch.ABB@wales.nhs.uk

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Aneurin Bevan University Health Board

COMPOSEd

Barriers to Effective **CO**-morbidity **M**anagement **POS**t-Strok**E**

CONSENT FORM (Stroke Survivors)

Trial Number: 238470 Centre:

Names of local Researcher:

Please initial in all the boxes (Please do not Tick) after each statement and sign below

I confirm that I have read and understood the participant information sheet (version 2.0 10/01/18) related to this study. I have had the opportunity to consider the information, ask questions and I am satisfied with the answers I have received.	
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	
I agree to answer a series of questions and take part in discussions as part of a focus group.	
I agree to be **audio recorded** during the focus group as part of this study.	
I agree that the research team may use **anonymous direct quotations** of anything I say during the focus group.	
I understand that my information will be kept confidential and the data collected is anonymous. It will only be looked at by individuals from the research team. I give permission for the research team to have access to the data I give as part of this study.	
I understand that my personal information may be checked by a regulatory authority, this may include checking my consent form, medical records and accessing the trial data. I am aware that this will be completed without violating my confidentiality.	
I agree to take part in the study as outlined to me and I know who to contact if I have any questions about the study in general.	

Please complete and return this consent form to the researcher. The consent form will be stored securely by the research team.

Name of Participant Date Signature

This study is funded by NHS Wales, Stroke Implementation Group.
10/01/18 – Participant Information Sheet Version 2.0 (238470)

Page **1** of **1**

[Patient]

Supplemental Figure 5-1. Stroke survivors consent form and invitation letter.

5.1.2 Healthcare professionals

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E-bost / e-mail – StrokeResearch.ABB@wales.nhs.uk
GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Aneurin Bevan University Health Board

COMPOSEd

Barriers to Effective **CO**-morbidity **M**anagement **POS**t-Strok**E**

CONSENT FORM (Healthcare Professionals)

Trial Number: 238470 Centre:

Name of local Researcher:

Please initial in all the boxes (Please do not Tick) after each statement and sign below

I confirm that I have read and understood the participant information sheet (version 3.0 22/01/18) related to this study. I have had the opportunity to consider the information, ask questions and I am satisfied with the answers I have received.	
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting me negatively in any aspect of my personal or professional life.	
I agree to answer a series of questions and take part in discussions as part of a focus group.	
I agree to be **audio recorded** during the focus group as part of this study.	
I agree that the research team may use **anonymous direct quotations** of anything I say during the focus group.	
I understand that my information will be kept confidential and the data collected is anonymous. It will only be looked at by individuals from the research team. I give permission for the research team to have access to the data I give as part of this study.	
I understand that my personal information may be checked by a regulatory authority, this may include checking my consent form and accessing the trial data. I am aware that this will be completed without violating my confidentiality.	
I agree to take part in the study as outlined to me and I know who to contact if I have any questions about the study in general.	

Please complete and return this consent form to the researcher. The consent form will be stored securely by the research team

Name of Participant Date Signature

This study is funded by NHS Wales, Stroke Implementation Group.
22/01/18 – Participant Information Sheet Version 2.1 (238470)

[Healthcare Professional]

Supplemental Figure 5-2. Healthcare professionals consent form and invitation letter.

5.2 Participant information sheet

Ymchwil Strôc – Stroke Research
Ffôn / Phone – 01633 238 228/ 238 729
E-bost / e-mail – StrokeResearch.ABB@wales.nhs.uk

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Aneurin Bevan University Health Board

COMPOSEd

Barriers to Effective **CO**-morbidity **M**anagement **POS**t-Strok**E**

Participant Information Sheet

You are being invited to take part in a research study that will involve your participation in a face-to-face focus group.

Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully to decide whether or not you wish to take part.

What is the purpose of the study?

The research study is interested in stroke survivors' experiences and opinions of diabetes management after a stroke. By taking part in this study you will be helping us to improve services for patients and shaping the direction of stroke research. The aim of the research study is to understand how stroke survivors currently feel about diabetes management. The research study will also explore stroke survivors' opinions of new forms of diabetes management.

What condition will this study cover?

The study is seeking participants who are stroke survivors who also have type II diabetes.

Where will this study be undertaken?

The study is being carried out in **Aneurin Bevan University Health Board** which is your local NHS Health Board.

If you decide to participate, then you will need to contact a member of the research team who will be able to tell you where and when a focus group is taking place.

Your normal scheduled appointments will not change if you decide to take part and taking part in this study will not affect your care now or in the future.

This study is funded by NHS Wales, Stroke Implementation Group.
10/01/18 – Participant Information Sheet Version 2.0 (238470)

Why have you been asked to take part?

Your own clinical team has found that you are potentially eligible to take part in this study. They have decided this because you have been diagnosed with a **stroke** and you have **type II diabetes**.

What will happen if I take part?

If you decide you would like to take part in the research you will need to contact the research team on the number provided. You will have an opportunity to ask any questions you may have and inform the research team that you would like to participate in the study. The research team will then invite you to take part in a focus group.

A focus group is a type of group discussion. A researcher will sit in the group and ask each person the same question and then the group will have the opportunity to discuss those answers. The researcher will ask a number of questions about your experiences of diabetes management after a stroke. There will be around 5 other stroke survivors who also have diabetes in the focus group. The focus group will last about an hour.

The researcher will record the focus group. The researcher will only record the audio of the focus group. During the focus group we will not use your real name so that your answers cannot be traced back to you. The recordings will be sent safely and securely to a professional transcription service. The transcription service will turn the audio recording into written dialogue known as a transcript. The research team will check that the transcripts are correct and are accurate. Once the checks have taken place and if the transcripts are accurate the research team will securely destroy the original audio recordings.

[*You have the right to request a transcript of your involvement in the focus group at any time. You may withdraw any answers given or alter any answers given at any time.*]

After the original audio recordings are securely destroyed then all the answers you give in the focus group will be **anonymous**. This means that any information you provide will remain completely confidential and cannot be traced back to you. The research team will do this as quickly as possible and will not keep the original audio recording longer than 3 months after the focus group.

To allow the research team to understand the background of participants, the research team will ask you in private about your background such as your Age, Sex, and the Type of Stroke.

Once the study is complete, the **anonymous results** of the study including **anonymous direct quotations** will be published in scientific journals and the research team will let your care team know the results.

To ensure the research team are conducting the study appropriately your personal information may be checked by a regulatory authority, this may include checking your

consent form, study data and medical records. This will be completed without violating your confidentiality.

Whether you decide or not to participate in the study, your care will not be affected now or in the future.

Will I be compensated for my time?

The research study is able to offer you a flat rate of £40 to cover any travel expenses you might incur and for your time. Please provide the research team with your details after the focus group to ensure you receive this. No payment shall be made prior to the focus group and payment shall only be made if you attend the entire focus group session. Please be advised it is your responsibility to declare this payment for tax or benefit purposes.

What are the possible benefits of taking part?

The benefits of taking part in this study;

- You will able making a contribution, which may influence the future direction of diabetes management after a stroke.
- You will also have the opportunity to influence the direction of future research and new diabetes management techniques after stroke.
- This means that by offering your thoughts and opinions you will be putting stroke survivors' voices front and centre.

Will the information I provide be kept confidential and are there any limits to confidentiality?

All the information you provide during the focus groups will be kept strictly confidential. The only limits to this confidentiality are disclosures of care you received that could be understood as misconduct, medical negligence or serious discrepancies/ issues in your care. Any disclosures of such nature will be referred via the appropriate channels and the research team may or may not contact you directly depending on the nature of the information you have disclosed. Whilst this is likely to be a very rare occurrence, you should be mindful of the limits of confidentiality before taking part and before volunteering answers or contributing to focus group discussions.

[***Please note:*** *that if you received care that you are unhappy with, which you believe should be subject to a formal complaint or have begun a formal complaints procedure that this study is not an appropriate platform to disclose any details of that care. If you would like any information about your local NHS complaints procedure please contact the complaints team on the number provided.*]

How long is the study running for?

The study is running between **November 2017** and **May 2018**. If the research team doesn't hear from you after **2 working weeks**, it will be assumed that you do not want to participate. The research team will not contact you again after that time.

Your participation is entirely voluntary, you can refuse to participate or withdraw from the study at any time without any affect to your future medical care. If you decide to withdraw from the study all data collected about you will be erased.

If for any reason you wish to make a complaint or have any concerns with regard to any aspect of the study please contact the Putting Things Right team on 01633 431674 or e-mail puttingthingsright.ABHB@wales.nhs.uk

Thank you for taking the time to read this information sheet and considering taking part in the study.

If you agree to participate in the study please call the Research Team on 01633 234 923

Or

E-mail: strokeresearch.abb@wales.nhs.uk

This study is funded by NHS Wales, Stroke Implementation Group.

Supplemental Figure 5-3. Participant information sheet.