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Assessing the impact of immunosuppressive therapies on the risk of hypertension

A thesis By

Hani Eid Alosaimi

BSc,MSc

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) to the Institute of Cardiovascular and Metabolic Health, College of Medical, Veterinary and Life Sciences, University of Glasgow

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Institute of Cardiovascular and Metabolic Health

College of Medical, Veterinary, and Life Sciences University of Glasgow

ABSTRACT

Background

Although it has a significant impact on morbidity and mortality, hypertension is a major global health concern that is frequently neglected. Despite its prevalence, the role of inflammation in hypertension is often overlooked. However, earlier research suggested a link between hypertension and specific inflammatory biomarkers, proposing that these biomarkers may play a pivotal role in the development and progression of hypertension. This was initially observed through the effects of immunosuppressive therapies, which were found to affect development of hypertension. This led to a growing interest in the role of inflammation in hypertension and its potential as a therapeutic target.

Inflammation is now recognised as an important contributor to the development and progression of hypertension. The immune system plays a key role in regulating inflammation and dysregulation of the immune response can lead to chronic low-grade inflammation that can contribute to hypertension and target organ damage. As a result, there is a growing interest in developing anti-inflammatory drugs to treat hypertension, particularly in patients who have not responded to traditional blood pressure-lowering medications.

Methodology for answering the research questions: Systematic review and meta-analysis of randomised-control trials (RCTs). It aimed to assess pre-specified outcomes including hypertension risk and evaluated particular pre-specified subgroups of patients, including drug subclasses, comparator drugs, population clinical setting and follow-up duration. This analysis was designed to investigate the differential varying benefits and risks when comparing different classes of immunosuppressive therapies.

Results

The thesis is divided into seven main results chapters (Chapters 4 to 10) based on the immunosuppressive therapies classes evaluated for risk of hypertension in the systematic review and meta-analysis. Risk was assessed in comparison to placebo or separately to other active drugs used to treat immune/inflammatory disorders. Altogether, the qualitative and quantitative analysis includes 141 RCTs that enrolled 60,580 participants in total with an average follow-up of 3.5 years.

Methotrexate (MTX) and risk of hypertension: This meta-analysis found that when Methotrexate (MTX) was compared to the placebo, there was no significant difference in the risk of hypertension (RR = 0.93, 95% CI, 0.61; 1.44, P = 0.75). Meanwhile, low and non-statistically significant heterogeneity between studies (I^2 = 14%, P = 0.33). When MTX was compared to other active drugs, MTX reduced the hypertension risk (RR = 0.47, 95% CI, 0.34; 0.65, P = 0.00001), while heterogeneity was observed between studies (I^2 = 29%, P = 0.11). These findings suggest that compared to other active drugs, MTX may reduce the risk of hypertension, but no significant difference was found when it was compared to a placebo.

Tumornecrosis factor inhibitors (Anti-TNF) and risk of hypertension: The findings for anti-TNF inhibitors were significantly different. The risk of hypertension was elevated for participants on anti-TNF inhibitors compared to those given a placebo (RR = 1.31, 95% CI 1; 1.73, P = 0.05); however, low heterogeneity was observed between studies (I^2 = 2%, P = 0.43). Meanwhile, when compared with other active drugs, the hypertension risk did not significantly differ (RR = 1.14, 95% CI 0.73; 1.78, P = 0.56) and minimal heterogeneity was observed between studies (I^2 = 38%, P = 0.11)**.** These results suggest that while the use of anti-TNF inhibitors may increase the risk of hypertension compared to a placebo, this difference is not statistically significant when compared to other active drugs.

Interleukin – 17 inhibitors (Anti-IL17) and risk of hypertension:
This study's meta-analysis showed that the risk of hypertension was not significantly different between Anti-IL17 and a placebo drug (RR = 1.09, 95% CI 0.75, 1.58, P = 0.65). Similarly, the risk of hypertension was not significantly different between Anti-IL17 and other active drugs (RR = 0.89, 95% CI 0.60, 1.31, P = 0.54). This analysis observed low heterogeneity between studies comparing Anti-IL17 to a placebo drug (I^2 = 9, P = 0.34), as well as between studies that compared Anti-IL17 to other active drugs (I^2 = 9, P =0.33). The present study's findings suggest that Anti-IL17 drugs do not significantly increase the risk of hypertension compared to placebo or other active drugs.

Interleukin – 6 inhibitors (Anti-IL6) and risk of hypertension:
In the Anti-IL6 group, the results of the meta-analysis found no statistically significant difference in the risk of hypertension between Anti-IL6 and a placebo (RR = 1.2, 95% CI 0.82; 1.73, P = 0.35) also finding no heterogeneity between studies (I^2 = 0%, P = 0.89). When Anti-IL6 was compared to other active drugs, this study found no statistically significant difference in the risk of hypertension between groups (RR = 1.48, 95% CI 0.97; 2.25, P = 0.07) and observed low heterogeneity between studies (I^2 = 7%, P = 0.37). Thus, this study's results showed that in both groups (placebo and active drugs), there was no significant increase in the risk of hypertension.

Purine and Pyrimidine synthesis inhibitors and risk of hypertension:
There was no statistically significant difference in the risk ratio when the results of the Purine and Pyrimidine synthesis inhibitors groups were compared to the placebo group (RR = 1.37, 95% CI 0.78; 2.44, P = 0.28) and no heterogeneity was observed between studies (I^2= 0%, P = 0.96). However, Purine and Pyrimidine synthesis inhibitors can reduce the hypertension risk when compared to other active drugs (RR = 0.81, 95% CI 0.65; 0.99, P = 0.04), while substantial heterogeneity

could be observed between studies (I^2 = 76%, P = 0.00001). These findings suggest that Purine and Pyrimidine synthesis inhibitors may be effective in reducing the risk of hypertension when compared to other active drugs, although no significant difference was found when compared to a placebo.

Interleukin 1 Beta inhibitors (Anti-1B) and risk of hypertension:
The results of this paper's analysis for Anti-IL 1B showed that compared to the placebo group, the risk of hypertension was not significantly different between the groups (RR = 0.74, 95% 0.35; 1.6, P = 0.45) and no heterogeneity was observed between studies (I^2 = 0%, P = 0.87). These findings suggest that the use of anti-IL 1B drugs does not significantly affect the risk of hypertension compared to a placebo.

Colchicine and risk of hypertension : The present study compared the impact of colchicine and the placebo on the risk of hypertension and found no significant differences between the groups (RR = 0.50, 95% CI 0.10; 2.38, P = 0.38), also finding no heterogeneity between studies (I^2 = 0%, P = 0.96). When colchicine was compared to other active drugs, the present study did not observe any statistically significant differences in the risk of hypertension between groups (RR = 0.44, 95% CI 0.09; 2.11, P = 0.31) and found low heterogeneity between studies (I^2 = 35%, P = 0.21). These results suggest that the use of colchicine does not significantly affect the risk of hypertension compared to either a placebo or other active drugs.

Conclusions

The overall risk of hypertension associated with each of the seven groups of drugs differs, with anti-Interlukin-6 agents, anti-Interlukin-17, anti-Interleukin-1beta and colchicine appearing not to affect the risk of the occurrence of hypertension when compared to either a placebo or other active drugs. In contrast, both Methotrexate and Purine and Pyrimidine synthesis inhibitors appear to reduce the risk of hypertension in comparison to other anti-inflammatory treatments. Anti-TNF medications, in turn, may borderline increase the risk of developing hypertension compared to placebo. The groups also differ in their heterogeneity with some having very low heterogeneity, while others have significant internal differences; nevertheless, most are highly homogeneous, with the results of similar studies being almost identical. These findings have important implications for clinical practice, suggesting that when healthcare professionals select immunosuppressive therapies for their patients, they should take into account the hypertensive effect those therapies have. Medications that inhibit the synthesis of purine and pyrimidine or methotrexate might be suitable choices for patients who have an elevated higher risk of hypertension. Further research is needed to understand the long-term effects and clinical significance of these findings, as well as to explore mechanisms, patient-specific factors, and the potential benefits or risks associated with specific populations or treatment durations. Overall, this study contributes valuable insights that may guide clinical decision-making, as well as stimulate further research in the fields of immunosuppression therapies and hypertension.

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Author’s declaration

I declare that this thesis and the work presented in it are my own work, unless specified otherwise in the text, and that this thesis has not been submitted previously for a degree or any other qualification at this University or any other institution.

Definitions/abbreviations

<	Greater than
=	Equal to
>	Less than
≤	Less than or equal to
≥	Greater than or equal to
ABC	ATP-binding cassette
ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AD	Alzheimer's disease
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AHA	American Heart Association
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
AKT	Protein kinase B
AMP	Adenosine monophosphate
ASC	Apoptosis-associated speck-like protein containing a CARD
BL	Baseline
BMI	Body mass index
BP	Blood pressure
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CAPS	Cryopyrin-associated periodic syndromes
CD	Cluster of differentiation
CD	Cluster of differentiation
CDC	complement-dependent cytotoxicity
CI	Confidence interval
CI	Confidence interval
CNO	Chronic nonbacterial osteomyelitis
CNS	Central nervous system
COVID	Coronavirus disease
COX	Cyclooxygenase
CRP	C-reactive protein
CVD	Cardiovascular disease

CVE	Cardiovascular event
DBP	Diastolic blood pressure
DHFR	Dihydrofolate reductase
DHODH	Dihydroorotate dehydrogenase
DMARD	Disease-modifying antirheumatic drug
DMD	Duchenne muscular dystrophy
DOCA	Deoxycorticosterone acetate
DOCA	Deoxycorticosterone acetate
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESRD	End-stage renal disease
EU	European Union
FCAS	Familial cold autoinflammatory syndrome
FDA	U.S. Food and Drug Administration
FE	Fixed-effects
FEM	Fixed-effects model
FMF	Familial Mediterranean fever
GFR	Glomerular filtration rate
HBPM	Home blood pressure monitoring
HFD	High-fat diet
HTN	Hypertension
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICU	Intensive care unit
IFN	Interferon
II	Indoleamine 2,3-dioxygenase
IL	Interleukin
IMPDH	Inosine monophosphate dehydrogenase
ITT	Intention-to-treat
JIA	Juvenile idiopathic arthritis
JNC	Joint National Committee
JNK	c-Jun N-terminal kinase
LEF	Leflunomide
MCP	Monocyte chemoattractant protein

MFS Marfan syndrome

MIS Multisystem inflammatory syndrome

MKD Mevalonate kinase deficiency

MMF Mycophenolate mofetil

MMP Matrix metalloproteinase

MPA Mycophenolic acid

MSU Monosodium urate

MTX Methotrexate

MWS Muckle-Wells syndrome

NALP NACHT, LRR, and PYD domains-containing protein

NF Nuclear factor

NICE National Institute for Health and Care Excellence

NK Natural killer

NKC Natural killer cell

NO Nitric oxide

NOS Nitric oxide synthase

NSAID Nonsteroidal anti-inflammatory drug

PC Primary care

PICOS Population, Intervention, Comparison, Outcome, Study design

RA Rheumatoid arthritis

RA Rheumatoid arthritis

RAAS Renin-angiotensin-aldosterone system

RAS Renin-angiotensin system

RCT Randomized controlled trial

RCT Randomized controlled trial

RE Random effects

REM Random-effects model

RIS Random-effects inverse variance

RR Relative risk

RR Risk ratio

SAA Serum amyloid A

SAID Systemic autoinflammatory diseases

SBP Systolic blood pressure

SH Subgroup analyses

SHR Spontaneously hypertensive rat

SLE	Systemic lupus erythematosus
SOD	Superoxide dismutase
TB	Tuberculosis
TIMP	Tissue inhibitor of metalloproteinases
tm-TNF	Transmembrane TNF-α
TNF	Tumor necrosis factor
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TPMT	Thiopurine S-methyltransferase
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome
UA	Uric acid
UCB	Union Chimique Belge
UK	United Kingdom
US	United States
USFDA	United States Food and Drug Administration
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
WKY	Wistar-Kyoto

Poster's presentations

Abstracts for poster presentation

Alosaimi, H., Maffia, P., Padmanabhan, S. and Guzik, T., 2022. **ASSESSING THE IMPACT OF IMMUNOSUPPRESSIVE THERAPIES ON INCIDENCE OF HYPERTENSION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OTHER AUTOIMMUNE DISEASES: A SYSTEMATIC REVIEW.** *Journal of Hypertension*, *40*(Suppl 1), pp.e41-e41.

Alosaimi, H., Maffia, P., Padmanabhan, S. and Guzik, T., 2023. **THE ASSOCIATION BETWEEN INTERLEUKIN-1 BETA INHIBITORS AND HYPERTENSION RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS.** *Journal of Hypertension*, *41*(1), pp.e227-e228.

Alosaimi, H., Maffia, P., Padmanabhan, S. and Guzik, T., 2023. **THE ASSOCIATION BETWEEN PURINE AND PYRIMIDINE INHIBITORS AND THE RISK OF HYPERTENSION: SYSTEMATIC REVIEW AND META-ANALYSIS**. *Journal of Hypertension*, *41*(1), pp.e228-e228.

Alosaimi, H., Maffia, P., Padmanabhan, S. and Guzik, T., 2023. **THE ASSOCIATION BETWEEN COLCHICINE AND HYPERTENSION RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS**. *Journal of Hypertension, 41(Suppl 3):p e228*

1. Introduction

1.1 Hypertension

1.1.1 Definition of hypertension

Hypertension (high blood pressure) is characterized by persistently raised blood pressure, which causes the target organ damage including cardiac, renal, vascular and central nervous system complications. Hypertension is defined as systolic blood pressure equal to or above 140 mmHg and/or diastolic blood pressure equal to or above 90 mmHg (WHO, 2013).In 2017, the American College of Cardiology and the American Heart Association redefined hypertension as systolic blood pressure equal to or above 130 mmHg and/or diastolic blood pressure equal to or above 80 mmHg (Mayfield et al., 2022) .

Blood pressure was initially described by Dr. Stephen Hales in 1733 , Hale measured arterial pressure by inserting glass tubes into horses arteries. However, the recognition and understanding of hypertension as a medical condition progressed significantly over time (Vertes et al., 1991). One key milestone was the discovery of the technique of auscultatory blood pressure measurement by Dr. Nikolai Korotkoff a Russian physician. The auscultatory blood pressure measurement technique remains a widely used to date (Paskalev et al., 2005).

There are several factors that can contribute to the development of hypertension. One of the factors that causes the development of hypertension is unhealthy lifestyle choices such as sedentary lifestyle, poor dietary habits (Senapati et al., 2015). The second is genetics where individuals with a family history of hypertension are at a higher risk of developing the condition (Ranasinghe et al., 2015). Age is the third factor with aging being associated with a higher risk of hypertension (Buford, 2016). The fourth is that certain medical conditions and chronic diseases such as chronic kidney disease, and diabetes increase the likelihood of hypertension development. Finally, increased blood pressure levels could be caused by prolonged periods of stress (Hamrahian and Falkner, 2017).

1.1.2 Significance of hypertension as a major public health issue

Hypertension is a major public health issue because it is the leading risk factor for cardiovascular disease and early death. The condition is the leading cause of mortality and disability-adjusted life year globally and only comes second to smoking as the leading cause of cardiovascular deaths (Oliva, 2019). Hypertension is also associated with high economic burdens. A study that assessed the total cost of hypertension in 15 countries (Brazil, Cambodia, Canada, China, Greece, Indonesia, Italy, Jamaica, Kyrgyzstan, Mexico, Poland, Spain, USA, Vietnam, and Zimbabwe) reported a total cost of 630.14 Int$ per person (Wierzejska et al., 2020). Based on the data extracted from 33 articles, Gnugesser et al. (2022) noted that the cost of treating uncomplicated hypertension was as high as 193.55$.

Hypertension is characterized by widening health disparities. Hypertension disproportionately affects certain populations including older adults, individuals with certain genetic predispositions and those from socioeconomically disadvantaged backgrounds (Oliveros et al., 2020, Mayfield et al., 2022).For example, In the US African Americans have a higher prevalence of hypertension compared to other demographics (Mayfield et al., 2022, Muntner et al., 2020).Racial health disparities associated with hypertension could be linked to the fact that more Whites with hypertension (48.2 %) have controlled blood pressure compared to the proportion of hypertensive African Americans (41.5 %). Similarly blood pressure control is higher among those with private and Medicare insurance compared to those without (Muntner et al., 2020). In developed countries where the proportion of the elderly is on the rise, the risk posed by hypertension to public health is set to increase because the prevalence of the condition is higher among the aging. For example, in the US more than 25 % of the population will be aged above 65 years , It should be noted that about 60 % of individuals aged above 70 develop high blood pressure (Oliveros et al., 2020).

The management of hypertension is challenging because it often has no warning signs or symptoms. Therefore, people with hypertension, who have not been checked are likely to suffer in silence and eventually die. It should be noted that uncontrolled high blood pressure could have devastating effects on the heart and may lead to malfunctioning of the kidneys (WHO, 2013). Hypertension is also a significant public

health issue because it is associated with cognitive impairment negatively impacting the quality of life. Hypertension contributes to aging and elevated risk of vascular cognitive impairment and Alzheimer's disease (Ungvari et al., 2021).

The other reason hypertension is a significant public health issue is associated with its preventability and modifiability. Hypertension is potentially preventable and modifiable through lifestyle changes and proper management. The public health challenge posed by hypertension is set to increase if adequate steps are not taken to address the increasingly predominant behaviors and lifestyles such as tobacco use, unhealthy diet and excessive use of salt, physical inactivity, obesity and harmful use of alcohol. The highlighted unhealthy lifestyle choices and behaviors could have devastating effects, especially among populations with genes that predispose them to hypertension. Public health policies should focus on the prevention of hypertension because high blood pressure is preventable at early stages through lifestyle changes. Additionally, hypertension is treatable through the use of medication and lifestyle modification. Certain exercise and relaxation routines also help in the management of mental challenges associated with high blood pressure (WHO, 2013).

1.1.3 Measurement and diagnostic procedures

There are different approaches used in the measurement and the diagnosis of hypertension, which are outlined in **Table 1-1**. One of the measurements is the clinic measurement that involves the use of an automated device or a manual sphygmomanometer to take blood pressure readings (Mancia and Grassi, 2014). Clinic measurement is carried by a healthcare professional and can occur in the doctor's office or a clinic. The determination of blood pressure in clinic measurement involves taking of two readings and calculating the average readings. However, the initial reading could be considered sufficient if it indicates a significantly high blood pressure (Pickering et al., 2005).

Ambulatory Blood Pressure Monitoring (ABPM) is the other approach that could be used to measure the blood pressure. Measurement of the blood pressure using ABPM involves an automated wearable portable device that monitor the blood pressure at certain intervals throughout a 24-hour period including the daytime and nighttime (Pena-Hernandez et al., 2020). For the daytime ABPM, the blood pressure is taken at regular intervals during waking hours or the active times of the day. The daytime

ABPM is important in the determination of the blood pressure levels during daily activities. The nighttime ABPM is also termed as nocturnal ABPM and it involves the measurement of blood pressure at regular intervals through the night. The nighttime ABPM is vital in the assessment of the nocturnal blood pressure dipping, which is key in the identifying of underlying health conditions (Mancia and Grassi, 2014). Home Blood Pressure Monitoring (HBPM) is carried out using a home blood pressure monitor usually at home. The HBPM readings are vital in assessing blood pressure patterns and could also provide insights regarding the potential white coat hypertension (George and MacDonald, 2015).

The measurement and diagnostic procedures of hypertension adopted by the United Kingdom (UK), Europe and the United States (US) have some variations in the thresholds. The National Institute for Health and Care Excellence (NICE), UK body that is mandated with developing evidence-based health guidelines has put forward blood pressure thresholds for clinic ABPM and HBPM measurement. As shown in Table 1, NICE guidelines of 2022 recommends that the diagnostic thresholds for hypertension in the UK for clinic measurement are systolic blood pressure (SBP) equal to or greater than 140 mmHg and/or diastolic blood pressure (DBP) equal to or greater than 90 mmHg. For ABPM (daytime) and HBPM measurements, the diagnostic thresholds for hypertension recommended by NICE are SBP equal to or greater than 135 mmHg and/or DBP equal to or greater than 85 mmHg (NICE, 2022).

In Europe, the diagnostic thresholds for hypertension are developed by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). As shown in Table 1, ESH/ESC recommendations of 2018 indicates that the diagnostic thresholds for hypertension for office measurement are SBP equal to or greater than 140 mmHg and/or DBP equal to or greater than 90 mmHg which is similar to the UK guidelines. The ABPM (daytime) and HBPM diagnostic thresholds recommended by ESH/ESC are similar to that of NICE. Additionally, ESH/ESC recommendations of 2018 provide diagnostic thresholds for ABPM (night time) as SBP equal to or greater than 120 mmHg and/or DBP equal to or greater than 70 mmHg and ABPM (24-hour) as SBP equal to or greater than 130 mmHg and/or DBP equal to or greater than 80 mmHg and ABPM (Volpe et al., 2019).The Eighth Joint National Committee (JNC 8), American Heart Association (AHA) and the American College of Cardiology (ACC) provide hypertension management guidelines and diagnostic thresholds in the US. The JNC 8 (2014)

recommends diagnostic thresholds for clinic/office hypertension measurement that is similar to ESH/ESC and NICE recommendations. However, ACC/AHA guidelines of 2017 recommend SBP equal to or greater than 130 mmHg and/or DBP equal to or greater than 80 mmHg. Similarly, ACC/AHA guidelines regarding HBPM and ABPM diagnostic thresholds indicating SBP equal to or greater than 130 mmHg and/or DBP equal to or greater than 80 mmHg differ from ESH/ESC and NICE (Kollias et al., 2022).

Table 1-1 Summary of the measurement and diagnostic procedures in the US, UK and Europe.

NICE (2022) - United Kingdom	
Clinic	SBP ≥140 and/or DBP ≥90
ABPM (Daytime)	SBP ≥135 and/or DBP ≥85
HBPM	SBP ≥135 and/or DBP ≥85
ESH/ESC (2018) - European	
Office BP	SBP ≥140 and/or DBP ≥90
ABPM	
Daytime	SBP ≥135 and/or DBP ≥85
Night time	SBP ≥120 and/or DBP ≥70
24-hour	SBP ≥130 and/or DBP ≥80
HBPM	SBP ≥135 and/or DBP ≥85
JNC 8 (2014) - US	
Clinic/Office	SBP ≥140 and/or DBP ≥90
ACC/AHA (2017) - US	
Clinic/Office	SBP ≥130 and/or DBP ≥80
ABPM	SBP ≥130 and/or DBP ≥80
HBPM	SBP ≥130 and/or DBP ≥80
Abbreviation: NICE: The National Institute for Health and Care Excellence; ESH/ESC: Eu Society of Cardiology/European Society of Hypertension; JNC: Joint National Committe ACC/AHA: American College of Cardiology/the American Heart Association.	

1.1.4 The global burden of hypertension

Recent studies have drawn attention to the mounting burden of hypertension all across the globe and its distressing and damaging consequences. Noncommunicable diseases (NCDs) – which include cardiovascular disease (CVD), diabetes, chronic respiratory disease and cancers – are not only the major causes of avoidable disease, disability and death, but also constitute 75 per cent of the 56.5 million deaths from all causes, reported from around the world in 2019. Just under a third of these deaths in that same year, totalling 18.6 million people, were ascribed to CVD. The most significant risk factor for CVD is known to be raised blood pressure (BP) or hypertension, which resulted in 10.8 million deaths -19.2

per cent of total deaths in 2019 – and 9.3 per cent of the disability-revised life years which were lost, globally (Schutte et al., 2021).

The last thirty years have seen the issue of how to deal with raised blood pressure among the population spread from high-income countries (HICs) to low and middle-income countries (LMICs) - including Sub-Saharan Africa and South and East Asia. Statistics from 2015 demonstrate that 23 per cent of the 1.3 billion adults known to have high BP live in South Asia (of whom 199 million live in India) and a further 21 per cent (235 million) are located in East Asia (Di Cesare et al., 2017).

Although not all the estimated figures in international surveys concur, it is clear that the incidence of elevated SBP (≥110-115 and ≥140 mm Hg) rose sharply between 1990 and 2015.This, in turn, was reflected in a rise in DALYs and deaths linked to elevated SBP. Using this sample as a basis for projections, it indicates that , in 2015, approximately 3.5 billion adults had SBP of at least 110 to 115 mm Hg, while 874 million adults had SBP of 140mm Hg, or even higher (Forouzanfar et al., 2017).

In the Middle East and North Africa (MENA) region, 30 per cent of the adult population is affected by hypertension - although this figure varies widely between individual countries. This prevalence rate was mirrored by the population of 140,000 individuals who were screened as part of MMM , when it was determined that only 31.9 per cent of people with hypertension were being monitored and treated (Schutte et al., 2023).The incidence of hypertension fluctuates from region to region and country to country. While it is more widespread among older adults, it can also affect younger individuals.

1.2 Immune system

1.2.1 Association between serum inflammatory biomarkers and incidence of hypertension

Evidence indicates varying findings between the serum inflammatory biomarkers and the incidence of hypertension. Sesso et al. (2015) noted that the increased plasma inflammatory markers and D-dimer were not significantly associated with an increased risk of hypertension in middle-aged and older men; they defined hypertension as SBP ≥140 mm Hg and/or DBP of ≥90 mm Hg. The researchers based

their prospective nested case-control study on data from 396 cases of incident hypertension and controls who free of hypertension. However, it should be noted that the cohort had low levels of plasma inflammatory markers, which suggests that the cohort was initially healthy and normotensive. In a nested case-control study conducted as part of the Women's Health Initiative Observational Study, Wang et al. (2011) reported no significant association between high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumour necrosis factor receptor (TNF) with incident hypertension. The researchers based their observation on data from 800 cases of incident hypertension along with 800 matched controls; the study included an equal number of White and Black women. However, the study was limited by the use of a single baseline measurement of each biomarker, which biased the outcome towards the null.

Sesso et al. (2007) reported that among women, CRP is strongly associated with hypertension risk while IL-6 has a weak association. In their prospective, nested case-control study involving middle-aged and older women with normal blood pressure, the researchers observed that higher plasma levels of IL-6 were initially linked to an increased risk of developing hypertension. But the association turned nonsignificant when BMI was incorporated into the model. Conversely, higher plasma CRP levels maintained a strong association with an increased risk of hypertension, albeit to a lesser extent, when BMI was added to the model. Further examination of IL-6 and CRP revealed that CRP maintained a strong association with hypertension risk, while IL-6 did not contribute significantly to predictive power beyond CRP.

According to Gordon et al. (2021), Leptin, TNFα and MCP-1 are positively associated with the risk of hypertension. Their study analysed data collected from 471 postmenopausal women (mean age = 65). Importantly, they noted that the covariates, such as smoking history and body mass, modified the association between the reported proinflammatory biomarkers and the risk of hypertension in an inconsistent manner.

To investigate the potential association between CRP levels and the occurrence of incident hypertension, Sesso et al. (2003) carried out a prospective cohort study that involved 20,525 US health professionals aged 45 years and above. The researchers defined hypertension as SBP ≥140 mm Hg and/or DBP of ≥90 mm Hg. Also noted that CRP is associated with an increased risk of hypertension development.

Madhur et al. (2010) conducted a study using IL-17-deficient mice (IL-17/) to investigate the impact of IL-17 on blood pressure. The researchers observed a similar hypertensive response to an angiotensin II infusion in both IL-17/ mice and C57BL/6J mice. However, unlike the wild-type mice, the IL-17-deficient mice did not sustain hypertension. In fact, after four weeks of angiotensin II infusion, their blood pressure levels were consistently 30-mm Hg lower than it was of the wild-type mice. Additionally, when examining IL-17 levels in diabetic individuals, the serum levels of this cytokine were found to be significantly higher in those with hypertension compared to normotensive subjects. Therefore, the researchers concluded that IL-17 plays a crucial role in maintaining angiotensin II-induced hypertension, suggesting it could be a potential therapeutic target. Table 1-2 illustrates the relationship between the inflammatory biomarkers and hypertension.

Table 1-2 Summary of examples of studies on how the levels of serum inflammatory biomarkers are associated with the presence of hypertension.

Study	Biomarker	Sample Size	Findings
(Wang et al., 2011)	CRP, IL6, IL1B and TNF-r2	36043	CRP, IL-6, IL-1, and TNF-r2 did not significantly correlate with the development of incident hypertension in white or black women.
(Bautista et al., 2005)	TNF and IL6	196	TNF-alpha and IL-6 could increase the risk of the development of essential hypertension.
(Abramson et al., 2002)	CRP	9867	Higher CRP levels are associated with an increased risk of hypertension in healthy US adults.
(Abramson et al., 2006)	CRP and TNF	140	Higher CRP and TNF levels are associated with increased blood pressure variability.
(Sesso et al., 2015)	CRP and TNF	396	Higher CRP and IL-6 levels are not associated with an increased risk of hypertension in middle-aged and older men.
Sesso et al. (2003)	CRP	20 525	Higher CRP levels associated with increased risk of hypertension in women, but not men.

1.2.2 Role of immune system in hypertension

Hypertension is considered to be a multifactorial condition, the development and progression of which is mediated by immune components. These components include the immune cells (T cells, and B cells) and molecules, such as cytokines and chemokines, which are involved in the pathogenesis of hypertension. Inflammatory processes promote changes in the endothelial cells, vascular system and renal cells,

leading to increased blood pressure (Rodriguez-Iturbe et al., 2017). The infiltration of immune cells to the organs, such as the kidneys, heart and blood vessels, results in inflammation and subsequent damage to the organs (Barhoumi et al., 2011, Guzik et al., 2007, Kasal et al., 2012, Schiffrin, 2015). The immune system plays a part in hypertension mainly through oxidative stress and dysregulation of the renin-angiotensin-aldosterone system (Rodriguez-Iturbe et al., 2017).

1.2.3 Pathophysiology of hypertension induced by immunity

The pathophysiology of hypertension induced by immunity involves a complex interplay between immune system dysregulation and various mechanisms, which contribute to elevated blood pressure as illustrated in Figure 1-1. Hypertension can occur as a result of the infiltration of the immune cells into the blood vessels, causing chronic low-grade inflammation. Immune cells, particularly T cells, monocytes and dendritic cells, infiltrate the perivascular and adventitia of blood vessels, releasing proinflammatory cytokines such as IL-17, TNF-alpha and IL-6 (Barhoumi et al., 2011, Guzik et al., 2007, Kasal et al., 2012, Rodriguez-Iturbe et al., 2017). The infiltration results in increased vasoconstriction arising from the remodelling of vessel walls, impaired endothelial-dependent vasorelaxation, and norepinephrine (Barhoumi et al., 2011, Guzik et al., 2007, Kasal et al., 2012, Schiffrin, 2015). Therefore, the infiltration of immune cells into the blood vessels contributes to increased peripheral resistance and elevated blood pressure.

The renin-angiotensin system (RAS) also plays a significant role in immune-mediated hypertension. Components of RAS, such as angiotensin and renin, regulate blood pressure and fluid balance (Rodriguez-Iturbe et al., 2017). There is a bidirectional interaction between RAS and the immune system (Crowley et al., 2010). For example, angiotensin II stimulates the production and release of proinflammatory cytokines including IL-6, TNF-alpha and IL-1β, which play important roles in inflammation and immune responses. On the other hand, immune cells, including macrophages promote the production of angiotensin II through the elevated expression of angiotensin-converting enzyme (ACE) (Rodriguez-Iturbe et al., 2017). Elevated levels of angiotensin II increase the release of aldosterone and the retention of sodium and water, leading to a rise in blood pressure (Franco et al., 2007). According to Navar et al. (2002) and Navar (2004), the activation of the intrarenal RAS by the immune cells

plays a key role in the development of hypertension. It increases the production of angiotensin II and the subsequent elevated blood pressure could also result from renal inflammation. Experiments involving spontaneously hypertensive rats indicate that the impairment in the pressure-natriuresis occurs due to renal inflammation inducing an increase in the intrarenal angiotensin II activity (Franco et al., 2013).

Oxidative stress resulting from immune system activation and inflammation, also contributes to immune-mediated hypertension. As noted by Los et al. (1995), oxidative stress plays a crucial role in the activation of proinflammatory signalling pathways and transcription factors, and stimulates lymphocyte function. On the other hand, inflammation intensifies the generation of excessive amounts of reactive oxygen species, which damage blood vessels, impair nitric oxide bioavailability and promote vasoconstriction. The absence of control over the production of reactive oxygen species, coupled with impaired antioxidant defence mechanisms, leads to vascular dysfunction and hypertension (Rodriguez-Iturbe et al., 2017).

The action of oxidative stress on the central nervous system also explains the development of angiotensin II-induced hypertension. Studies have shown that increased superoxide dismutase (SOD) activity in circumventricular organs alters the recruitment and infiltration of activated T cells around blood vessels, influencing the development of hypertension (Zimmerman et al., 2004). Angiotensin II can induce hypertension by acting directly, or through reactive oxygen species, to increase proinflammatory cytokines in the CNS (Shi et al., 2010, Sriramula et al., 2008).

The sympathetic nervous system is a critical link between the CNS and the immune system, and it can also participate in the induction of hypertension (Rodriguez-Iturbe et al., 2017). The over activity of the sympathetic nervous system can lead to elevated blood pressure through increased sympathetic outflow (Esler, 2000), renal sodium retention, direct vasoconstriction (Dibona, 2004), activation of the RAS (Kobori et al., 2010), enhanced cardiac output (Navar, 2014) and the promotion of oxidative stress and inflammation (Carnevale et al., 2014, Elenkov et al., 2000). It is evident that the pathophysiology of hypertension induced by immunity involves a multifaceted interaction between immune system dysregulation, inflammation, RAS activation, autoimmunity, oxidative stress, altered sodium handling and sympathetic nervous system hyperactivity. These mechanisms result in impaired vascular activity, elevated peripheral resistance and increased blood pressure.

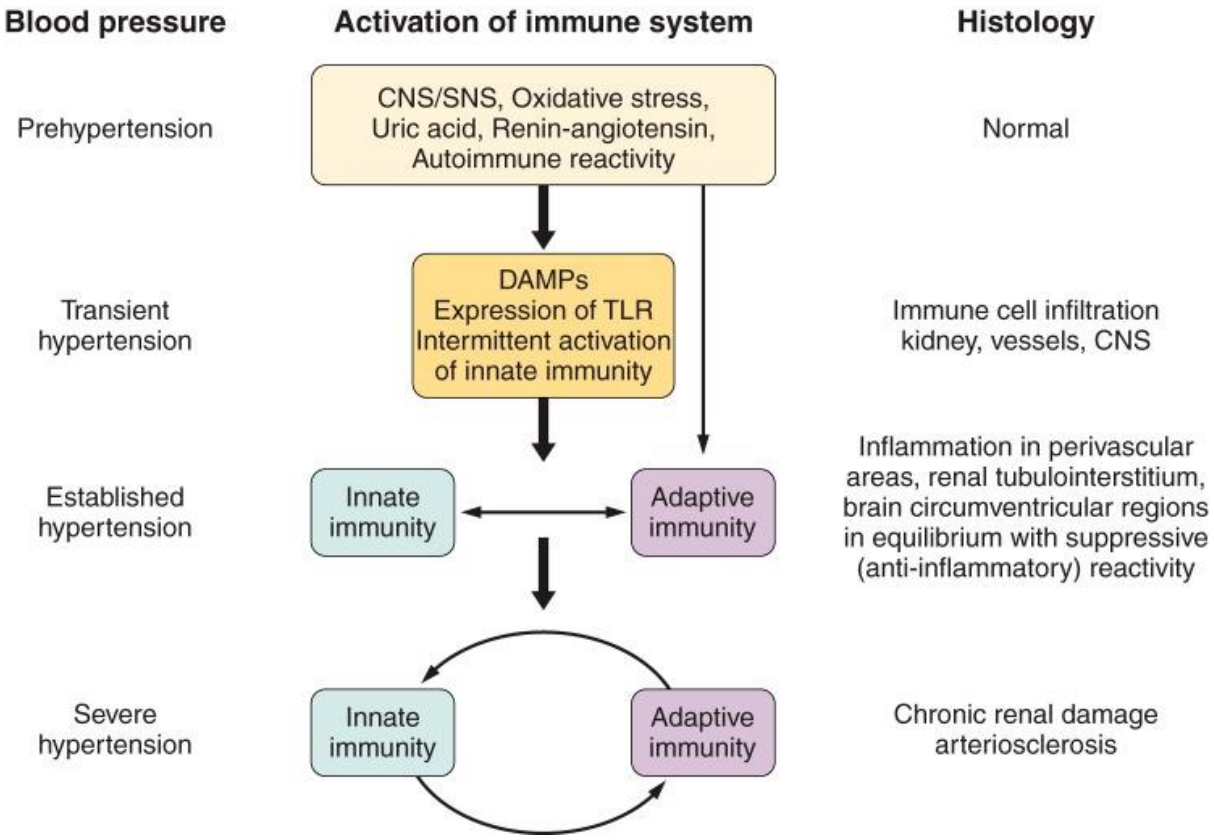

Figure 1-1 Pathophysiology of hypertension induced by immunity adapted from Rodriguez-Iturbe et al. (2017).

1.3 immunosuppressive therapies

1.3.1 Influence of immunosuppressive therapies on blood pressure

immunosuppressive therapies suppress or modulates the immune system's activity. Evidence suggests that immunosuppressive therapies could be used to treat hypertension induced by immunity. In this section, a number of papers focusing on pharmacology of inflammatory and immunosuppressive medications were studied.

Diverse autoimmune diseases are treated with drugs that inhibit specific targets, such as IL-1ß, IL-6, IL-17, TNF, purine and pyrimidine (such as leflunomide, mycophenolate, and azathioprine), or with antagonists, such as methotrexate and colchicine.

Although some studies find the risk of hypertension is reduced by medications, such as methotrexate, other drugs, such as leflunomide, are reported to raise blood pressure (Hadwen et al., 2021b). Zhao et al. (2015) found that some patients taking the TNF inhibitors, certolizumab pegol and etanercept, had an elevated risk of hypertension. Saleh et al. (2016) reports tha IL-17α inhibitor reduce blood pressure as well as limiting renal/vascular inflammation. However, blood pressure does not respond to these drugs uniformly, with different drugs having different effects upon different individuals. Mangoni et al. (2017a) highlights that multiple factors influence he therapeutic indications for these medications, including the patient's individual response to the intervention and the particular condition being treated. The effect of medications upon blood pressure must be a factor that healthcare professionals consider when determining treatments for their patients.

Methotrexate (MTX) is an anti-inflammatory drug used by patients with rheumatoid arthritis to control symptoms and enhance the survival rate .The drug works mainly by targeting the pro-inflammatory state in rheumatoid arthritis (Weinblatt, 2013). The use of MTX as an anti-inflammatory therapy among patients with rheumatoid arthritis and those with chronic inflammation is characterized by diminished cardiovascular events, which suggests that the drug could have protective cardiovascular effects (Micha et al., 2011, Roubille et al., 2015)

Mangoni et al. (2017a) examined clinic and 24-hour peripheral and central BP levels in rheumatoid arthritis patients receiving MTX treatment (n = 56, age 61 ± 13 years, 70% females) and compared them to those not taking MTX (n = 30, age 63 ± 12 years, 76% females), noted that the MTX treatment group had significantly lower clinic and 24-hour peripheral and central blood pressure compared to those not receiving MTX, linked the observed reduction in blood pressure to the variations in pulse wave velocity.

The reduction in blood pressure due to MTX treatment could also be linked to adenosine-induced direct vasodilation (Koupenova et al., 2012). It should be noted that MTX treatment promotes the accumulation of adenosine by inhibiting the enzyme aminoimidazole carboxamide ribonucleotide transformylase, which triggers pathways that leads to reduced adenosine catabolism (Cutolo et al., 2001).

According to Van Rhee et al. (2015), the use of interleukin (IL)-6 blocking agents such as Siltuximab is associated with adverse events including hypertension. Based their conclusion on a study that assessed the tumor and symptomatic responses among patients with Multicentric Castleman disease. The researchers noted that three among the 19 patients who received Siltuximab treatment 5 years had symptoms of hypertension. Therefore, conclude that hypertension is one of the adverse events associated with Siltuximab treatment.

Tumor necrosis factor-alpha inhibitors such as infliximab inhibit the biological activity of TNF-α by binding to both the soluble and transmembrane forms of TNF-α, therefore, hindering the binding of TNF-α to its receptors (Scallon et al., 1995). Abdelrahman et al. (2018) carried out experiments with rats that were fed a 60% fructose diet in the absence or presence of infliximab. The researchers noted that in the absence of infliximab fructose significantly increased blood pressure. However, the administration of infliximab attenuated the fructose-induced increase in blood pressure. Therefore, concluded that infliximab could be used in reversing fructose-induced high blood pressure. Gazzoto Filho et al. (2013) demonstrated the effects of infliximab on systolic blood pressure in their study that involved Male Wistar Kyoto rats (WKY) and spontaneous hypertensive rats (SHR) who were divided into six groups of tens. Following eight weeks of treatment with infliximab, as has been noted that the infliximab administration effectively prevented the elevation of systolic pressure and the development of left ventricle hypertrophy in SHR.

Klarenbeek et al. (2010) reported a reduction in blood pressure among patients with recent-onset rheumatoid arthritis who received infliximab. based their conclusion on data collected from 508 patients who were randomized into four groups with one consisting of patients who were treated with step-up combination therapy with infliximab.

Saleh et al. (2016) demonstrated that the genetic deletion of interleukin (IL)-17A resulted in blunted hypertension and Limited renal and vascular dysfunction. based their study on Wild-type C57BL/6J mice aged 10 to 12 weeks that received Ang II infusion to induce hypertension. The mice in the experimental group received IL-17A neutralizing antibody, IL-17F neutralizing antibody, and IL-17RA receptor antagonist, study observed that acute pharmacological inhibition of interleukin-17A (IL-17A) or the interleukin-17 receptor A (IL-17RA) receptor subunit exhibited the potential to

significantly lower blood pressure by approximately 30 mm Hg. The researchers further noted that the inhibition demonstrates a notable capacity to diminish renal and vascular inflammation while also reducing markers associated with renal injury and fibrosis. The observed effectiveness of IL-17A targeting in the management of hypertension could be linked to the fact that interleukin exerts regulatory control over the renal sodium chloride cotransporter via activation of the serum and glucocorticoid regulated kinase 1 pathway (Norlander et al., 2016).Saleh et al. (2016) indicated that IL-17A signaling, specifically through the interleukin-17 receptor A (IL-17RA) subunit plays a pivotal role in the development of angiotensin II-induced hypertension and consequential end-organ damage. Therefore, concluded that IL-17A and IL-17RA receptor subunit inhibition is an appealing therapeutic avenue for the effective management of hypertension.

Madhur et al. (2010) also indicated the critical role of IL-17 in the maintenance of angiotensin II-induced hypertension and vascular dysfunction noting that IL-17 may hold potential as a therapeutic target for the management of this prevalent disease. Based their conclusion on a study conducted utilizing IL-17−/− mice. observed that the mice with hypertension had a significant increase in serum IL-17 concentrations compared to normotensive subjects.

Orejudo et al. (2019) also suggested that therapeutic strategies targeting IL-17A should be explored as potential interventions to prevent kidney injury induced by hypertension. suggestion is based on the findings of their study that involved experimental models with adult male C57BL/6 mice and clinical data and human renal biopsies (n = 20). Study noted that following 14 days of IL-17A infusion in mice, blood pressure exhibited a notable increase compared to control mice, concomitant with the infiltration of inflammatory cells, including CD3+ and CD4+ lymphocytes, as well as neutrophils, within the kidneys. Furthermore, upregulation of proinflammatory factors and intracellular mechanisms associated with inflammation were observed in the kidneys of the mice that received IL-17A infusion. However, there was a reduction in inflammatory cell infiltration in the kidneys of the mice that received anti-IL-17A neutralizing antibodies, and also noted the presence of Th17 and T lymphocytes (IL-17A-positive cells) in the kidney biopsies of patients with hypertensive nephrosclerosis further suggesting the pathogenic role of IL-17A in inflammation associated with hypertensive kidney disease.

Egeberg et al. (2018) carried out Phase 3 clinical trials of ixekizumab, employing a randomized, double-blind, and placebo-controlled study design. Data on vital signs, including blood pressure and pulse, were collected at each visit. There were no significant deviations noted in systolic and diastolic blood pressure after a duration of 60 weeks.

According to Rothman et al. (2020), canakinumab-mediated inhibition of IL-1β does not affect blood pressure or the development of hypertension. The researchers noted that although IL-1β inhibition has cardiovascular benefits, the benefits are independent of blood pressure modulation or the prevention of incident hypertension. based their conclusion on a study that involved 10,061 patients with a history of myocardial infarction and high sensitivity C-reactive protein (hsCRP) levels ≥2 mg/L, who were randomly assigned to receive canakinumab at doses of 50 mg, 150 mg, 300 mg, or a placebo. Among the 9,549 participants with recorded blood pressure measurements during the follow-up period, 80% had a preexisting diagnosis of hypertension.

Purine and Pyrimidine inhibitors such as Leflunomide and mycophenolate are involved in hypertension in various ways. There are concerns regarding the impact of leflunomide treatment on blood pressure elevation. Based on a prospective study that involved 30 patients with rheumatoid arthritis treated with standard doses of leflunomide, study noted a statistically significant increase in systolic blood pressure as early as 2 to 4 weeks into the treatment , therefore, emphasized the need for regular blood pressure measurements during leflunomide treatment (Rozman et al., 2002) .

Evidence suggests that Mycophenolate, an immunosuppressive drug, could help to reduce the risk of hypertension. Moes et al. (2018) examined the vascular and renal tubular effects of mycophenolate in the DOCA-salt model in rats for a duration of 4 weeks. The researchers noted that the administration of mycophenolate is associated with the attenuation of blood pressure elevation with a significant reduction in telemetric mean arterial pressure observed from day 11 onwards, culminating in lower levels after 4 weeks of treatment compared to the control group. Furthermore, noted that when co-administered with the DOCA-salt model, mycophenolate effectively prevents the DOCA-salt model-induced angiotensin II type 2 receptor-mediated vasoconstriction.

Additionally, Cao et al. (2019) in their meta-analysis noted that mycophenolate therapy could potentially play a role in blood pressure regulation. study provided evidence suggesting that treatment with mycophenolate may have a modest impact on reducing diastolic blood pressure while not affecting systolic blood pressure. Importantly, observed that mycophenolate therapy does not increase the risk of hypertension, thus highlighting its favorable cardiac safety profile in transplant patients.

Herrera et al. (2006) examined the effects of mycophenolate among patients with hypertension and normal renal function. The study involved eight patients who were assessed before initiating mycophenolate treatment, during mycophenolate treatment, and one month after discontinuing the treatment. Observed a significant reduction in systolic, diastolic, and mean blood pressure levels.

Although colchicine has been shown to improve systemic inflammation and limit cardiac dysfunction, there is little evidence showing a positive effect on blood pressure. Based on a study in which salt-sensitive rats were treated with a high-salt diet, Shen et al. (2022) reported enhanced survival and attenuated cardiac dysfunction as a result of colchicine administration. noted that colchicine treatment reduced oxidative stress and the infiltration of inflammatory cells. Based on their observations, study suggested that colchicine should be further examined for potential therapeutic potential in the management of hypertension.

Evidence from human studies suggests that colchicine does not show a positive effect on blood pressure. In a study that involved 31 Middle-aged men with essential hypertension, noted no effect on arterial pressure after 3-week colchicine treatment followed by a washout period (Ehlers et al., 2022).

The drugs of interest in this thesis are immunosuppressive therapies: colchicine, methotrexate, IL-1ß inhibitors, IL-6 inhibitors, IL-17 inhibitors, TNF inhibitors, and purine and pyrimidine inhibitors (such as leflunomide, mycophenolate and azathioprine). These drugs share the purpose of treating autoimmune diseases and preventing organ rejection following transplantation. However, dysregulated blood pressure is counted among the physiological effects associated with these medications. It is incumbent upon healthcare professionals to take into account

the potential effects that these drugs have upon a patient's blood pressure and to monitor it closely. Multiple factors should inform healthcare practitioner's choices of drugs and dosages; key factors include the condition being treated and the patient's response to treatment. To provide effective treatment, it is critical to appreciate the influence that these medications can have upon blood pressure.

1.3.2 A potential therapeutical target

Hypertension treatments should focus on limiting the infiltration of the immune cells into the blood vessels and subsequent vasoconstriction, increased peripheral resistance and elevated blood pressure (Barhoumi et al., 2011, Guzik et al., 2007, Kasal et al., 2012, Schiffrin, 2015) .The therapies should also target immune cells that promote increased production of Angiotensin II responsible for the retention of sodium and impairment in the pressure-natriuresis leading to a rise in the blood pressure (Franco et al., 2013, Rodriguez-Iturbe et al., 2017) .Furthermore, treatment should target pathways responsible for the production of reactive oxygen species such as the drugs that upregulate the production and activity of SOD (Zimmerman et al., 2004). Therapeutic strategies including targeting of IL-17A using anti-IL-17A neutralizing antibodies could help in addressing of angiotensin II-induced hypertension (Madhur et al., 2010). Immunosuppressants such as mycophenolate that deplete proliferating B and T lymphocytes should assessed for potential role in blood pressure regulation (Cao et al., 2019). Colchicine should also be examined for potential therapeutic potential in the management of hypertension, given the effect oxidative stress and the infiltration of inflammatory cells (Shen et al., 2022). Evidence also indicates that blood pressure decreased in patients that received infliximab, suggesting possible use in the treatment of hypertension (Klarenbeek et al., 2010). Focusing upon colchicine, methotrexate, IL-1β inhibitors, IL-6 inhibitors, IL-17 inhibitors, TNF inhibitors, and purine and pyrimidine inhibitors (such as leflunomide, mycophenolate and azathioprine) is appropriate, because these drugs are recognised as having the capacity to dysregulate blood pressure. For example, Mangoni et al. (2017a) undertook an observational study that explored the effect of methotrexate in rheumatoid arthritis patients; they identified a trend in which

hypertension was less prevalent and blood pressure was lower in patients taking the drug. In contrast, a putative relationship has been identified between TNF inhibitors and incident hypertension in ankylosing spondylitis patients (Liew et al., 2022). More recently, Zhang et al. (2023) reported the possibility of a causal association between interleukin 6 trans-signalling and the elevated risk of pulmonary arterial hypertension. Furthermore, Davis et al. (2021) suggest that IL-17α is a suitable target for the therapeutic management of hypertension, as it plays an essential role in the pathogenesis of the condition. Taken together, the evidence from these various studies highlight the presence of a relationship between these particular drugs and dysregulated blood pressure; thus, further exploration of the phenomenon is warranted.

1.4 Summary of literature review and study rationale

1.4.1 Overview of literature review

The reviewed literature posits that immunosuppressive therapies such as Methotrexate, TNF inhibitors, Interleukin 6 inhibitors, Interleukin 17 inhibitors, Interleukin 1B inhibitors, purine and pyrimidine inhibitors (including Leflunomide, Mycophenolate, and Azathioprine), and Colchicine, potentially elevate the risk of hypertension in specific patient populations. Nevertheless, the impact of these therapies on blood pressure remains equivocal with conflicting outcomes observed. The precise mechanisms underpinning the association between immunosuppressive treatments and hypertension remain inadequately elucidated. Plausible factors encompass alterations in vascular functionality, renal function modifications, and other physiological effects. Several risk factors have been identified that may augment the propensity for hypertension development in patients receiving immunosuppressive therapies. These factors encompass age, gender, pre-existing cardiovascular disease, obesity, and other comorbidities. However, it is important to note that the reviewed investigations delineate hypertension as an incidental outcome in conjunction with other conditions rather than as a primary endpoint.

1.4.2 Rationale for the study

The use of immunosuppressive therapies present potential implications on the progression of hypertension. Therefore, there is a compelling need to undertake further investigations to elucidate the intricate relationship between these pharmacological agents and blood pressure. The principal objective of this study is to assess the association between specific immunosuppressive therapies, including methotrexate, TNF inhibitors, interleukin 6 inhibitors, interleukin 17 inhibitors, interleukin 1b inhibitors, purine and pyrimidine inhibitors (such as leflunomide, mycophenolate, and azathioprine), and colchicine,the likelihood of hypertension development in patients afflicted with autoimmune disorders. The outcomes derived from this investigation could enhance clinical practice and augment patient outcomes by facilitating the identification of preventive and management strategies to address hypertension in patients undergoing immunosuppressive therapies. Collectively, the present study assumes paramount significance due to its capacity to address the gap within the current body of literature relating to the interplay between immunosuppressive therapies and hypertension. As result, this research stands to make important contributions towards refining the treatment and management approaches for patients with autoimmune disorders. The research outcome could also serve as an impetus for the identification of promising therapeutic intervention such as MTX for individuals with hypertension. The research outcome could also equip healthcare providers with crucial insights to effectively manage elevated blood pressure using the interventions being investigated.

1.5 Aim and objectives

1.5.1 Aim

To investigate the association between selected immunosuppressive therapies and the risks of hypertension.

1.5.2 Objectives

1) To assess the relationship between Methotrexate drug and the risk of hypertension.

2) To assess the relationship between Tumor necrosis factor inhibitors and the risk of hypertension.

3) To assess the relationship between Interleukin 17 inhibitors and the risk of hypertension.

4) To assess the relationship between Interleukin 6 inhibitors and the risk of hypertension.

5) To assess the relationship between purine and pyrimidine synthesis inhibitors and the risk of hypertension.

6) To assess the relationship between Interleukin 1 beta inhibitors and the risk

of hypertension.

7) To assess the relationship between Colchicine drug and the risk

of hypertension.

2. Methods

2.1 Systematic Review and Meta-Analysis

In this section, the methods employed to perform a systematic review on the seven main classes of immunosuppressive therapies used in RCTs were analysed. The key purpose of this is to examine the relationship between immunosuppressive treatments and the risks of hypertension. The reporting of this systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA-P) of 2015 (Moher et al., 2015). The protocol is registered with PROSPERO (ID: CRD42023427684) and can be accessed at https://www.crd.york.ac.uk/prospero/#recordDetails

2.1.1 Inclusion and Exclusion criteria (PICOS)

In order to determine which studies could be included in this review, the Population Intervention Comparison Outcome Study (PICOS) design framework (da Costa Santos et al., 2007) was employed. The PICOS strategy enabled the researcher to categorise search terms into thematic groups with the purpose of identifying medical literature to undergo systematic review. In this work, the standard search strategies of the immunosuppressive therapies review, as well as supplementary terms were employed to identify relevant studies.

2.1.1.1 Population

The study included men and non-pregnant women who were at least 18 years of age. Moreover, the participants may or may not have undergone previous treatment with immune suppressive agent. This study recruited patients who had hypertension, or who were being treated with anti-hypertensive medication. Inclusion criteria were identified and methods of obtaining and analysing data were selected for this population. The study's results might be of value to hypertensive patients and those who are receiving anti-hypertensive treatment.

Studies were excluded if the following populations were employed in the sample: pregnant women, individuals under 18 years of age, hospitalised patients, and people with pulmonary hypertension, ocular hypertension, cancer, or end-stage renal disease (ESRD) (eGFR 15-19 ml/min/1.73 m2). Moreover, studies involving participants who had undergone haemodialysis or suffered from inherited diseases (i.e., Duchenne muscular dystrophy (DMD), ribbing disease, polycystic kidney disease, Marfan Syndrome (MFS)) were excluded. Finally, any studies that lacked details pertaining to important population characteristics or healthcare settings were excluded from the review.

2.1.1.2 Interventions and Comparators (I & C)

This review included adult participants who had been treated with the seven major classes of immunosuppressive treatments (i.e., Anti-IL6, Anti-IL17, MTX, Anti-IL1B, Colchicine, Anti-TNF and Purine, Pyrimidine synthesis inhibitors) in various doses and sub-classes. The treatment could take the form of monotherapy or combination therapy and may be a stepped-care or non-stepped-care approach.

Combination drug treatments that included other immunosuppressant agents (e.g., Methotrexate, Anti-TNF or prednisolone) were permitted so long as one of the combined drugs used in the control group (e.g., Anti-TNF + drug X vs. drug X), was the same for both the intervention and comparator arms (Anti-TNF+ drug X vs. MTX+ drug X) and (Anti-TNF or MTX+ drug X vs drug X+ drug Y). Moreover, it was required that Drug X was administered at the same fixed or titrated dose in both arms.

Comparators such as placebo, DMARDs, and other anti-inflammatory medications (including MTX, Prednisolone, and leflunomide) were also permitted. The intervention and comparator medications could be administered orally, intravenously, or intramuscularly. Additionally, as part of a stepped therapy approach, additional medications from other classes were permitted following randomization. Nonetheless, these drugs had to be pre-determined and adhere to the identical procedure in both arms. Trials that have a history of using immunosuppressive medications were also considered eligible.

Moreover, studies that involved the following interventions and controls were excluded from the review: **1] Intervention:** immune system reducing drugs that were not immunosuppressant agents; trials comparing drugs belonging to the same class. **2] comparators:** trials comparing interventions involving non-pharmacological agents (diet, herbs, exercises, and surgical procedures).

These exclusion standards were used to produce an objective result. Background treatment with a non-Immunosuppressant was allowed in both arms of combination therapy. This method results in reduced bias in the outcomes of the included studies. As the conclusions of a review depend on the findings of the included studies, a meta-analysis is likely to produce false conclusions if the findings of the individual studies are biased. Another form of bias can be generated if studies that should have been included are omitted. This is known as publication bias. The risk of bias can be evaluated using accepted procedures, as mentioned in **chapter 2 ,section 2.1.8.7**. Moreover, the exclusion criteria serve to minimise bias in the findings of the included studies, which is critical for the review.

2.1.1.3 Outcome

This research aims to examine the impacts that immunosuppressive therapies have on hypertension. Thus, the studies involved in the review must report on hypertension as a negative effect in terms of number of events.

2.1.1.4 Study Type (S)

Only the RCTs that met the following criteria were permitted to be included in the present review: 1] double-blind RCTs or Prospective Randomized Open Blinded-Endpoint (PROBE) trials; 2] parallel or factorial-design; 3] single- or multicentre RCTs; 4] randomized trials in which the number of participants is not disclosed; 5] studies in which the median or average follow-up time is at least 12 weeks; and 6] conference abstracts that have detailed findings, as they provide

access to the most recent research, which helps to ensure the work is comprehensive in its scope. The conference abstracts were analysed carefully and the key findings pertaining to the relationship between immunosuppressive therapies and hypertension were extracted.

. Moreover, cross-over studies, observational studies (cohorts, case control, cross-sectional and case reports), subgroup studies, and post hoc analyses and quasi-experimental designs in which participants were not randomly assigned to treatment group were all excluded from the trials. This is because such studies involve randomization that is not performed on an individual level (cluster-randomized), when the same individual serves as a control (cross-over studies), and when the same individual becomes a research participant. Moreover, any studies that involved animals or that have been retracted were omitted from the review.

2.1.1.5 Geographical Location

In this review, studies carried out in other countries were included, so long as they focused on the seven main classes of immunosuppressive treatments that are commonly prescribed around the world. Thus, no language restrictions were employed during the search process. This study benefits from accessing a broad range of literature, including non-English language publications. Translation services and access to language experts was facilitated by the Glasgow University Library. By using these services, we could be confident that the translations and interpretations of the non-English language documents were reliable, which is essential to upholding integrity and accuracy of the work.

2.1.2 Search Strategy used to Identify Relevant Studies

2.1.2.1 Electronic Searching

The databases used to perform the search for relevant studies were: Cochrane Central Register of Controlled Trials (CENTRAL), the Medical Literature Analysis and Retrieval System Online (MEDLINE Ovid (1946 onwards), and the Excerpta

Medica Database (EMBASE Ovid (1974 onwards). Additionally, the the Cochrane Database of Systematic Reviews was also searched. A search was conducted to locate articles published within an unspecified time period. the search was modified and performed again on 17th June 2023.

In order to find higher quality evidence from a large body of literature indexed in certain medical databases, search filters were designed as the best possible tactics (Lefebvre et al., 2017). Medical Subject Heading (MeSH) terms and pertinent subject keywords to ensure that the search for studies was comprehensive. Moreover, Paul Cannon the Glasgow University librarian provided valuable assistance with creating Keywords. Thus, a review of the terms was done via Zoom, and he also made several comments and suggestions for improving the search. **Appendix A** provides a full description of the search technique used in this case.

2.1.2.2 Non-Bibliographic Database Search

In order to find relevant studies, drug names and/or classes were searched on a number of clinical trial registers, including www.ClinicalTrials.gov. ClinicalTrials.gov is an online register and results repository for clinical trials involving human subjects that have received both governmental and private funding and have been carried out all over the world. Moreover, references from identified articles (i.e., reviews and meta-analyses) were also checked. In the case that studies that did not list the frequency of hypertension events as an unfavourable outcome of interest, the authors were contacted by email. A second email was sent if no response was received within two weeks.

2.1.3 References Management

Using the EndNote Version 20 reference management software, the data and references created from the chosen electronic databases were imported and arranged into a bibliographic library. The endnote export (.enw) format or Research Information Systems (RIS) were both used to import all citations from electronic databases. Duplicates were located and then eliminated using the

EndNote 20 deduplication tool. In the duplicate reference library, duplicate records were kept. Additionally, after organising the references by title, duplicates were manually identified by examining the references. The documents were loaded into Rayyan QCRI (the Systematic Reviews web programme) in order to be scanned. This can be accessed at http://rayyan.qcri.org (Ouzzani et al., 2016). A free screening tool called Rayyan QCRI can be used to speed up the initial process of reviewing abstracts and titles while also identifying duplication. This tool makes a decision regarding whether a study should be included, excluded, or undecided and provides reasons. In turn, this web tool enables the identification of research that are eligible based on PICOS. Then, citations that needed to undergo full-text screening (i.e., those that were assigned as 'included' or 'undecided' were exported into EndNote format (.enw) and subsequently transferred to a Microsoft Excel (version 2019) spreadsheet for labelling. The bibliographic library was maintained and revised solely by the primary researcher (Hani Alosaimi).

2.1.4 Study Selection Process

2.1.4.1 Title and Abstract Screening

The primary researcher (Hani Alosaimi) evaluated the study titles and/or abstracts in accordance with the predetermined inclusion standards described in **section 2.1.1**. Several articles were rejected during the Rayyan QCRI screening procedure, and the reasons for those rejections were noted. These records were disregarded for one of two reasons: either they were obviously unrelated to the review topic or they failed to satisfy the pre-established standards. The complete text of the paper was retrieved where the eligibility condition was not evident from the title and/or abstract. Moreover, the two review authors (Hani Alosaimi and Rawabi Qadhi) independently evaluated the complete texts of each qualifying manuscript. A number of studies were rejected and explanations for those decisions were provided.

2.1.4.2 Obtaining Documents

The primary researcher consulted their library account and the Universtiy of Glasgow to search for full-text articles. If the library did not hold a full text article, then it was requested from the British Library Document Supply Service (BLDSS)-*The British Library* by the librarian. Finally, to obtain as many full-text articles as possible, additional sources were searched (i.e., the 'Google' web search engine) by title of article or name of journal.

2.1.5 Data Extraction

Hani Alosaimi and Rawabi Qadhi independently decided which trials should be included and what data should be retrieved from those trials. If necessary, any concerns or doubts were clarified by consulting the supervisory authors (Prof.Sandosh Padmanabhan and Prof. Tomasz Guzik). After determining how much data should be collected, the data collecting form was created. The information needed to evaluate study quality and gather evidence for synthesis was constructed as a collection form and entered into a normal Microsoft Excel 2019 spreadsheet. Data were extracted and collected using the PICOS framework (which considers the population, research design, intervention, comparators and outcome measures).

In terms of participant characteristics, the following details were examined: 1] the number of participants who had been treated with ITT approaches, 2] the number of participants randomized to each arm, 3] the clinical settings of the population, 4] baseline and achieved means SBP/DBP; 6] (mean age (years), male and female (%).

Additionally, the following intervention and comparators features were extracted: 1] drug class; 2] generic drug name; 3] control group; 4] drug dose; 5] background of immunosuppressant agents at randomization (%); 6] supplementary agents; and 7] compliance with treatment (%).

With regard to outcome measure, the following factors were considered: 1] outcomes as pre-defined or adverse events; 2] number of events for each assigned arm; 3] adjudication of outcome diagnosis; 4] source of data (published or unpublished); 4] data type.

In terms of research methodology, the following factors were considered: 1] research acronym; 2] full title of research; 3] research author's name; 4] year of publication; 5] journal publishing date; 6] research duration (total, mean or median); 7] quality domains of the methodology; 8] analysis type (ITT or per protocol); 9] predefined primary and secondary outcomes; 10] research sponsor.

2.1.6 Assessment of Methodological Quality

2.1.6.1 Risk of bias across domains

The "risk of bias" instrument is a domain-based evaluation tool that was employed in the present work to evaluate the risk of bias in accordance with the Cochrane Collaboration's guidelines (HIGGINS, 2017a). Through seven distinct domains, this tool enables bias to be critically assessed. These domains are as follows: (1) the generation of random sequences ; (2) the concealment of allocation sequences; (3) the blinding of participants and employees; (4) the assessment of outcome blinding; (5) completeness of outcome data; (6) selective outcome reporting; and (7) other bias sources. Each domain was assigned a grade of high, low, or uncertain risk of bias, with HIGGINS (2017a) providing the rationale for sticking to protocol during the assessment.

2.1.6.2 General Assesment of Bias Risk

Each study was rating in terms of low, high or unclear. Moreover, each outcome was evaluated separately for each study. To be more precise, the outcomes for all domains were evaluated in a similar manner. Thus, the risk of bias during the outcome assessment blinding domain was evaluated based on the subjective or objective nature of the outcome.

To determine the overall risk of bias based on the Cochrane Collaboration Guidelines, the risk of bias for each RCT was summarised. The key domains here were deemed to be sequence generation, allocation concealment and outcome assessment blinding. The significance of three areas of interest were evaluated through methodological research, namely sequence generation, allocation concealment) (Schulz et al., 1995; Wood et al., 2008), and blinding (Hróbjartsson et al., 2012). The RCT bias was thus rated as low if all key domains had low bias risk, high if at least one key domain had high bias risk, or unclear if at least one key domain carried an unclear bias risk but no evidence of high risk. The most significant risk of bias was determined to be present in studies with high or uncertain bias risk levels in one important dimension. Otherwise, they were believed to have a minimal bias risk.

The risk of bias was examined by two researchers (Hani and Manal), with any disagreements being resolved through discussion until a consensus was reached. It is important to note that studies were not eliminated from the review based on study quality.

2.1.7 Approach to Missing Data

Based on the Cochrane Collaboration Guidelines, a meta-analysis was carried out using an intention-to-treat (ITT) strategy (HIGGINS, 2017b). The following actions were taken to address incidents of missing data in published studies or supplemental material, data was acquired from ClinicalTrial.gov and other peer-reviewed publications, previous meta-analyses and other peer-reviewed publications.

2.1.8 Meta-Analysis

2.1.8.1 Meta-Analysis Software

The meta-analysis was conducted using the Review Manager 5 (RevMan 5.4) software, a program created by the Cochrane Collaboration Group that is designed to prepare and store Cochrane Reviews. The software is free for all Cochrane authors and can be used for academic purposes. This software uses two statistical models, namely a random-effects model (REM) and a fixed-effect model (FEM).

2.1.8.2 Fixed-Effect Model (FEM) Meta-Analysis

The Fixed-Effect Model (FEM) presupposes that all studies have the same true (common) effect size and that any variations in reported effects are due to sampling error (inaccurate effect size estimation). Since we have more knowledge on the same effect size in larger research, we may essentially ignore information from smaller studies when allocating weights to different studies. One genuine effect size is reflected in the combined effect estimate produced by the FEM. Within-study variance can be defined as the inverse of the weight given to each study. By giving weights to each research included in the analysis, sampling error and within-study error indicated by the distribution of points found in the meta-analysis can be lessened (Borenstein et al., 2010). Among the advantages of this model is its ability to estimate the common effect size reliably. Another advantage of the model is that studies are weighted in favour of larger, detailed ones; it also estimates the average effect size and confidence intervals. However, (Tufanaru et al., 2015) argues that the fixed-effect model cannot accommodate excessive heterogeneity, making it unsuitable when there are considerable differences between the studies.

2.1.8.3 Random-Effects Model (REM) Meta-Analysis

The Random-Effects Model (REM) assumes that study involved in a meta-analysis estimates a true effect that is unique to that study. Nonetheless, the REM does not estimate a single real effect in the same way that the FEM does, although it does assist in estimating the mean distribution of effects. Thus, the null hypothesis is that the average of these effects is either 1.0 for ratio or zero for difference. Two types of variation (i.e., within-study error and between-study variance (Tau2)) must be taken into account as REM estimates the mean distribution of effects (Borenstein et al., 2010). Furthermore, Tau2 is estimated using the DerSimonian and Laird Method of Moment (DerSimonian and Laird, 1986). Furthermore, the CI produced by REM is much wider than the FEM and the weight of each study is similar. As we examine the variations between the two models, distinct outcomes will become clear. Extreme studies will have less influence if they are huge and more influence if they are small as we transition from FEM to REM. Meta-analyses frequently use random-effects models; however, they are not without drawbacks. An important disadvantage of the model is that it assumes exchangeability, whereby the true effects come from a normal distribution, yet such an assumption might be unrealistic. A further drawback is that interpreting the data can be complex, particularly when the analysis is of only a few studies (Higgins et al., 2009). Therefore, when selecting a suitable model for a meta-analysis, it is important to consider the drawbacks carefully. On the other hand, random-effects models benefit from accommodating the heterogeneity of studies and having the ability to estimate the overall effect size and uncertainty realistically and conservatively (Dettori et al., 2022).

2.1.8.4 Data Synthesis: Treatment Effect and Model-Used Measurements

As recommended by the Cochrane Collaboration and PRISMA, a trial-level meta-analysis was carried out. The aggregated outcome data was considered to be dichotomous data, while the risk of the intervention was reported as a risk ratio (relative risk). The risk ratio (RR) and 95% confidence interval (CI) are determined by RevMan 5 according to the meta-analytic summary of DerSimonian and Laird (DerSimonian and Laird, 1986). When two requirements are satisfied, it

can be assumed that all studies are functionally equivalent. Furthermore, our purpose is to compute the common effect size of a tightly defined population that cannot be generalised to a wider range of circumstances. Thus, for these reasons, FEM is preferred. The studies employed in this review vary in several ways, particularly in terms of the subjects they include and how the interventions are carried out. The underlying effect sizes of the studies can also vary considerably. In order to calculate the summary effect size, REM would thus be a better choice (Borenstein et al., 2010, Barili et al., 2018).A Mantel-Haenszel FE model was used to confirm the findings and to prevent small studies from being unduly weighted. If some event rates and study sizes are low, the statistical characteristics of the Mantel-Haenszel FER should be employed. The RE model and the FE model produce the same outcomes if heterogeneity is not established. Each pooled RR was subjected to an analogous z test, with P 0.05 denoting statistical significance. The trial with no incidents was subjected to continuity correction (corrected automatically by RevMan 5.4) (Borenstein et al., 2010). Furthermore, the results were expressed as a percentage relative risk ratio (RRR): RRR=100% × (1−RR). A pooled RR of 1 (or near to 1) indicates little to no difference in risk. Meanwhile, an RR of >1 indicates an increased risk of a particular outcome in the exposed group. Finally, an RR of <1 indicates a lower risk in the exposed group. Additionally, funnel plots were visually assessed in order to evaluate publication bias.

2.1.8.5 Accuracy of Treatment Effect: Confidence Intervals

The 95% confidence interval (CI) for a relative risk (RR) estimate refers to the range in which we can be certain that a true population effect will be identified. The 95% confidence interval's width reveals how accurate the estimate is. A smaller CI denotes a more accurate population estimate, while a larger CI denotes a less accurate estimate. The width of the 95% confidence interval (CI) for a meta-analysis is determined by the accuracy of the estimations from each individual study and the total number of studies considered. The breadth of the 95% confidence interval (CI) gets smaller when more studies are included in a meta-analysis. Nonetheless,if heterogeneity increases after additional studies are included, then the width of the 95% CI will also increase under the random-effects model (see section 2.1.8.6). A logical relationship exists between the CI and P

value. If 95% CI includes 1, the significance test will generate a P value that is higher than 0.05. On the other hand, if the value 1 is not included in the 95% CI, then the p-value will fall below 0.05. If the p-value is exactly 0.05, then the upper or lower limit of the 95% CI will include the RR null value of 1 (SCHÜNEMANN, 2021).

2.1.8.6 Heterogeneity Assessment

Heterogeneity can be defined as variability between the studies involved in a systematic review. Given the range of the patients, interventions and outcomes evaluated, as well as the methodological variance in the research design and bias risk, such differences could be clinical (HIGGINS, 2017b). The clinical or methodological variability may be the cause of the statistical heterogeneity between risk estimations. Cochrane's chi-squared (x^2, or Chi^2) test (sometimes referred to as the Q-statistic test) is the most common statistical test employed to identify and quantify heterogeneity is (Borenstein M, 2009). It meausres assumptions that all studies share a common effect size (including homogeneity and the null hypothesis) (Higgins and Thompson, 2002) .

In this work, a statistically significant p-value of <0.05 demonstrates the heterogeneity of the intervention effects. It is well acknowledged that high power indicates clinically irrelevant heterogeneity between trials and that the Q-statistic test for heterogeneity can be low if one study is more accurate than the others (Hardy and Thompson, 1998).

Therefore, no test can be expected to determine the exact extent to which heterogeneity impacts a meta-analysis. In order to measure inconsistency between research, a different test known as the I^2 statistic was applied.

Higgins and Thompson (2002) explain that this refers to the proportion of effect estimate variability that results from heterogeneity as opposed to sampling error (chance). The number of studies included in the meta-analysis has no bearing on this outcome. The I^2 value can fall between 0% and 100%, with the former indicating no observed heterogeneity and the latter indicating high heterogeneity.

The following percentages serves as a rough guide that can be used to interpret I^2 (HIGGINS, 2017b): **0% to 40%:** may not be important; **30% to 60%:** could indicate moderate heterogeneity; **50% to 90%:** could indicate significant heterogeneity; and **75% to 100%:** indicates significant heterogeneity.

If I^2 is 50% or higher, significant heterogeneity is often regarded as being present. The RE meta-analysis method makes it easier to include between-study variability in an aggregate estimate when there is heterogeneity. Instead of addressing the heterogeneity, this approach takes into consideration variations in treatment efficacy between trials. To calculate the between-studies variance from the observed effect, this model used Tau^2 statistics. It is crucial to understand that even a non-significant test for heterogeneity does not ensure that all of the trials included in a meta-analysis are homogeneous (Higgins and Thompson, 2002). By using subgroup and sensitivity analyses, the present work effectively examines heterogeneity.

2.1.8.7 Bias Assessment of Studies

When there are relevant studies missing from the review, publication bias can occur. This is because they may subsequently remain unpublished (STERNE, 2006). In this work, the funnel plot was visually assessed in order to detect publication bias. A funnel plot can be defined as a simple scatter graph that demonstrates the intervention effect estimates from individual studies and plots them against a specific measure. In turn, it presents the size or precision of a study. In the graphical figure, the study size is shown on the vertical axis along with a triangular 95% confidence zone based on a fixed-effect model, and the horizontal line reflects the effect estimate (HIGGINS, 2017b). The spread would be wider for larger research, with effect estimates for smaller studies being near the bottom of any plot. The largest or most powerful ones will be found near the top of the plot. The plot will resemble an inverted funnel if bias does not exist. The model seemed symmetrical at the top (representing large studies) in the presence of bias, with more studies missing (small studies) closer to the bottom.

2.1.8.8 Sensitivity Analysis

To determine the reliability the estimated association between immunosuppressive therapies and the risk of hypertension, a sensitivity analysis was carried out. The purpose of this analysis was to assess the impact of particular criteria upon the results. Studies that had a small sample size, or a high risk of bias, or failed to achieve the 95% confidence interval threshold were excluded from the analysis. The sensitivity analysis was informative in determining the impact that excluding these studies had upon the overall findings; this is important, as it helps to affirm the reliability and validity of the study's results. Apart from a limited number of trials, the analyses are presented in detail in the methods section of each result chapter.

2.1.8.9 Subgroup Analysis

To explore the relationship between immunosuppressive therapies and the risk of hypertension, subgroup analyses were perormed. The following three factors were analysed: (1) comparator drugs, (2) clinical setting and (3) duration of follow-up. Analysing these subgroups enabled potential variations in the relationship between the drugs and the risk of hypertension to be identified. In turn, this promoted wider understanding of the impact that these factors could have upon immunosuppressive therapies initiating hypertension. The subgroup analyses are instructive, revealing nuances in the findings; furthermore, they are helpful in identifying possilbe sources of clinical and statistical heterogeneity. The methods section of each result chapter presents details about the stratified analysis.

3. Immunosuppressive therapies and risk of hypertension: screening, eligibility, and quality assessment

3.1 Aim

The current chapter presents the results arising from the systematic review, as well as an in-depth description of the particulars of the papers, both included and excluded, retrieved from the literature search. Additionally, the bias risk relating to the use of randomised clinical trials (RCTs) for the evaluation of the impact of immunosuppressive treatments on hypertension risk is discussed.

3.2 Search results

The search was carried out in accordance with the methods presented in Appendix A. 3574 records were identified from database sources that were both bibliographic and non-bibliographic. PRISMA flow diagram have been created in order to illustrate the approach to the search and the way in which the articles were processed in order to give the results for the individual groups (See **Figure 3-1**). The qualitative and quantitative syntheses performed for this review encompassed 141 trials; these included 620,580 subjects who met the inclusion criteria. **Sections 3.2.1** and **3.2.2** detail the trials which met the exclusion and inclusion criteria for the review, respectively.

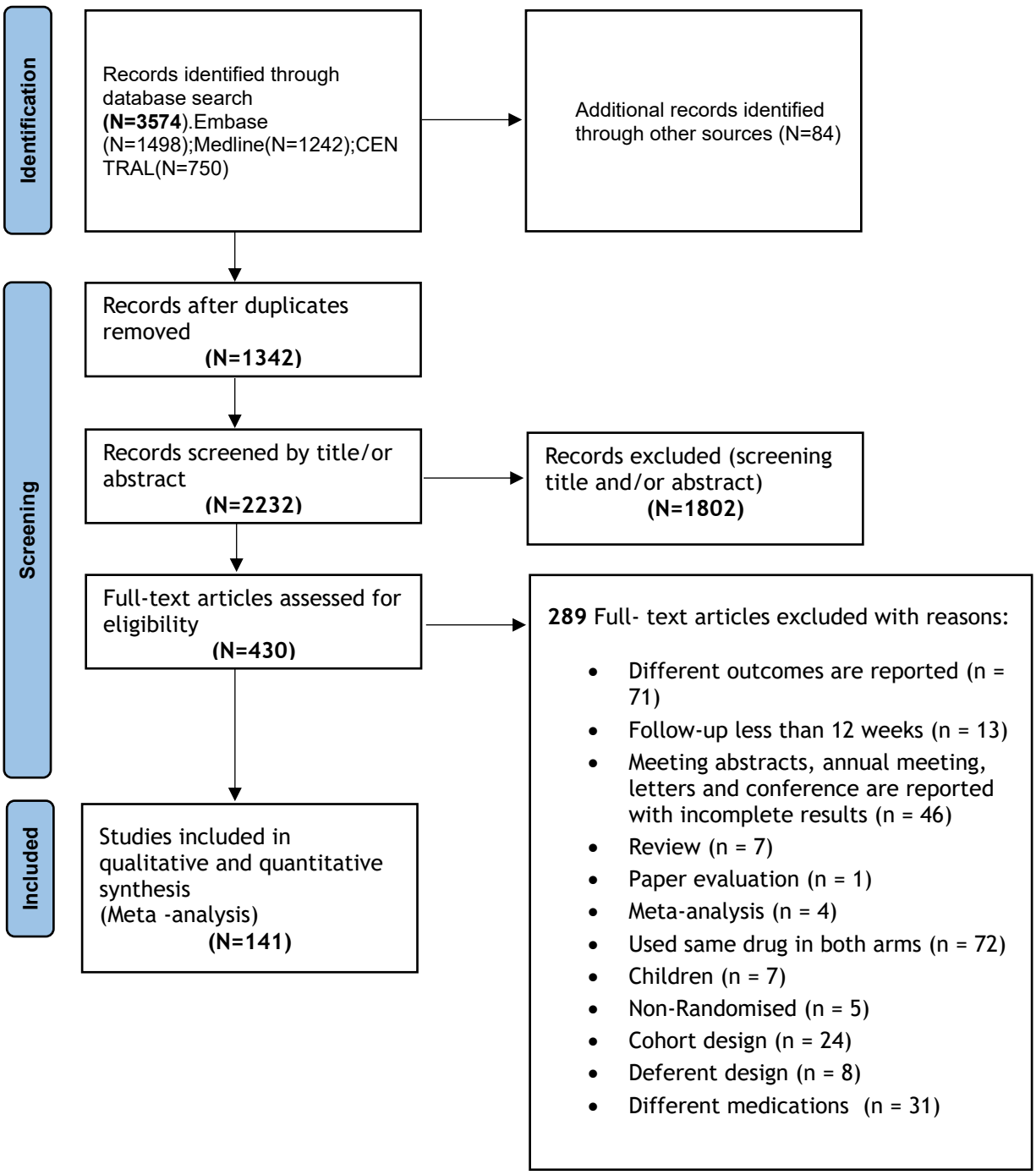

Figure 3-1 PRISMA study flow diagram

3.2.1 Description of excluded studies

The full texts of all the identified studies were screened. 289 studies failed to meet the inclusion criteria and were therefore excluded from the review; the reasons that they were discounted are listed in **Table 3.1**.

Table 3-1 Reasons for excluding studies

Trial	Reason for exclusion	Reference
POPE	Scientific abstract reported with incomplete results	(Pope et al., 2013)
VOLLENHOVEN	Meeting abstracts reported with incomplete results	(Van Vollenhoven et al., 2014)
ATZENI	Letters	(Atzeni et al., 2011)
BAKKER	Used same drug in both arms	(Bakker et al., 2012)
BALUOM	Different medications	(Baluom et al., 2011)
BATHON	Used same drug in both arms	(Bathon et al., 2011)
BAUGHMAN	Used same drug in both arms	(Baughman et al., 2000)
BINGHAM	Used same drug in both arms	(Bingham III et al., 2015)
BURMESTER	Cohort design	(Burmester et al., 2011)
BURMESTER	Different medications	(Burmester et al., 2017b)
CHEN	Used same drug in both arms	(Chen et al., 2013)
CHOPRA	Used same drug in both arms	(Chopra et al., 2016)
CIMMION	Conference	(Cimmino et al., 2008)
MRI	Used same drug in both arms	(Conaghan et al., 2016)
TREACH	Used same drug in both arms	(De Jong et al., 2013)
DERVIEUX	Different medications	(Dervieux et al., 2003)
DUGGAN	Used same drug in both arms	(Duggan and Keam, 2009)
DUNSMORE	Children	(Dunsmore et al., 2020)
EMERY	Used same drug in both arms	(Emery et al., 2008)
EMERY	Different medications	(Emery et al., 2017b)
LITHE	Used same drug in both arms	(Fleischmann et al., 2013)
FRASER	Used same drug in both arms	(Fraser et al., 2005)

OSKIRA-3	Meeting abstracts	(Genovese et al., 2013)
GISONDI	Non-Randomised	(Gisondi et al., 2020)
GREENWALD	Different medications	(Greenwald et al., 2011)
GROMMES	Used same drug in both arms	(Grommes et al., 2017)
HETLAND	Used same drug in both arms	(Hetland et al., 2006)
OPERA	Used same drug in both arms	(Hørslev-Petersen et al., 2016)
KAY	Used same drug in both arms	(Kay et al., 2015)*et*
KEYSTONE	Used same drug in both arms	(Keystone et al., 2008)
RAPID-1	Used same drug in both arms	(Keystone et al., 2012)
KONIJN	Abstract	(Konijn et al., 2016)
KREMER	Cohort design	(Kremer et al., 2004)
KREMER	Used same drug in both arms	(Kremer et al., 2006)
KREMER	Used same drug in both arms	(Kremer et al., 2002)
KREMER	Different medications	(Kremer et al., 2014)
KREMER	Used same drug in both arms	(Kremer et al., 2003)
KUME	Meeting abstracts	(Kume et al., 2011)
KUPERSMITH	Meeting abstracts	(Kupersmith et al., 1997)
LAN	Used same drug in both arms	(Lan et al., 2004)
LEUNG	Abstract	(Leung et al., 2010)
LOUGHRAN	Deferent design	(Loughran Jr et al., 1985)
MACHADO	Used same drug in both arms	(Machado et al., 2016)
MAHIDA	Meta-analysis	(Mahida et al., 2019)
MAINI	Different medications	(Maini et al., 1999)
MARCHESONI	Used same drug in both arms	(Marchesoni et al., 2003)
MARGUERIE	Follow-up less than 12 weeks	(Marguerie et al., 2002)
MEASE	Different medications	(Mease et al., 2012)
COMPONENT	Different medications	(Muehler et al., 2019)
MURATA	Review	(Murata et al., 2006)
OHSUGI	Paper evaluation	(Ohsugi, 2008)
PANAYI	Used same drug in both arms	(Panayi, 2005)
TRANSIT	Used same drug in both arms	(Paul et al., 2014)
PAVELKA	Different medications	(Pavelka et al., 2015)
POPOVIC	Different outcomes are reported	(Popovic et al., 1998)

OPTION	Review	(Ramos-Remus and Muriel-Vizcaino, 2008)
RATANATHARATHORN	Different medications	(Ratanatharathorn et al., 1998)
RAU	Used same drug in both arms	(Rau et al., 2004)
CIRT	Different outcomes are reported	(Ridker et al., 2018)
RINGDEN	Children	(Ringden et al., 1986)
RUEDA	Review	(Rueda et al., 2011)
RUPERTO	Used same drug in both arms	(Ruperto et al., 2016)
SAFY	Used same drug in both arms	(Safy et al., 2017)
SANDHU	Different outcomes are reported	(Sandhu et al., 2003)
CHAMPION	Used same drug in both arms	(Saurat et al., 2011)
SHIMADA	Used same drug in both arms	(Shimada et al., 2020)
COMPONENT	Annual meeting	(Sierakowski et al., 2011)
RAPID	Used same drug in both arms	(Smolen et al., 2009a)
SMOLEN	Used same drug in both arms	(Smolen et al., 2017)
OPTION	Different medications	(Smolen et al., 2008)
SMOLEN	Different medications	(Smolen and Emery, 2000)
GO-AFTER	Different medications	(Smolen et al., 2009b)
SOLOMON	Meeting abstracts	(Solomon et al., 2019)
TAKEUCHI	Different medications	(Takeuchi et al., 2016)
TAKEUCHI	Different medications	(Takeuchi et al., 2018b)
TANAKA	Different medications	(Tanaka et al., 2014)
TAYLOR	Different medications	(Taylor et al., 2019)
SIRROUND-H	Different medications	(Taylor et al., 2018)
TER WEE	Different medications	(ter Wee et al., 2015)
TESSER	Used same drug in both arms	(Tesser et al., 2019)
VAN DER	Different medications	(van der Heijde et al., 2019)
VOLLENHOVEN	Used same drug in both arms	(van Vollenhoven et al., 2012)
VANNI	Meeting abstracts	(Vanni et al., 2020a)
VANNI	Different outcomes are reported	(Vanni et al., 2020b)
MINCKWITZ	Used same drug in both arms	(Von Minckwitz et al., 2005)
WANG	Meta-analysis	(Huang et al., 2019b)
WANG	Used same drug in both arms	(Wang et al., 2020)

WEINBLATT	Used same drug in both arms	(Weinblatt et al., 2010)
GO-FURTHER	Used same drug in both arms	(Weinblatt et al., 2013)
WEINBLATT	Used same drug in both arms	(Weinblatt et al., 1999)
WESTHOVENS	Used same drug in both arms	(Westhovens et al., 2006)
WIJESINGHE	Used same drug in both arms	(Wijesinghe et al., 2017)
WOODMAN	Cohort design	(Woodman et al., 2017a)
WU	Used same drug in both arms	(Wu et al., 2020)
HIKARI	Used same drug in both arms	(Yamamoto et al., 2014a)
Anti-TNF		
POPE	Scientific abstract reported with incomplete results	(Pope et al., 2011)
ANGEL	Non-Randomised	(Angel et al., 2012)
ATZENI	Letters	(Atzeni et al., 2011)
BAGEL	Deferent design	(Bagel et al., 2012)
BINGHAM	Different outcomes are reported	(Bingham III et al., 2015)
BLAUVELT	Used same drug in both arms	(Blauvelt et al., 2021)
CHOE	Used same drug in both arms	(Cai et al., 2017)
DAVIS	Different outcomes are reported	(Davis et al., 2005)
DIRCKX	Different outcomes are reported	(Dirckx et al., 2013)
DUGGAN	Different outcomes are reported	(Duggan and Keam, 2009)
ELEWSKI	Different outcomes are reported	(Elewski et al., 2018)
EMERY	Different outcomes are reported	(Emery et al., 2009)
VENCOVSKY	Used same drug in both arms	(Emery et al., 2017a)
EMERY	Used same drug in both arms	(Emery et al., 2017b)
SYLWESTRZAK	Used same drug in both arms	(Emery et al., 2017c)
FARIA	Different outcomes are reported	(Faria et al., 2021)
JINHUA	Different outcomes are reported	(Fu et al., 2019)
FURST	Different outcomes are reported	(Furst, 2009)
GIARDINA	Used same drug in both arms	(Giardina et al., 2010)
GILES	Different outcomes are reported	(Giles, 2016)
GLATT	Used same drug in both arms	(Glatt et al., 2019)
GOTTLIEB	Meeting abstracts	(Gottlieb et al., 2020)
GRIFFITHS	Used same drug in both arms	(Griffiths et al., 2017)

HOLZER	Different outcomes are reported	(Holzer et al., 2021)
OPERA	Used same drug in both arms	(Hørslev-Petersen et al., 2016)
SYCAMORE	Different outcomes are reported	(Horton et al., 2019)
ISRCTN	Different outcomes are reported	(Isrctn, 2007)
JOBANPUTRA	Used same drug in both arms	(Jobanputra et al., 2012)
KAVANAUGH	Different outcomes are reported	(Kavanaugh et al., 2009)
KAY	Deferent design	(Kay et al., 2016)
KEYSTONE	Different outcomes are reported	(Keystone et al., 2008)
KEYSTONE	Used same drug in both arms	(Keystone et al., 2013)
KIMBALL	Different outcomes are reported	(Kimball et al., 2011)
LAN	Different outcomes are reported	(Lan et al., 2004)
LEE	Deferent design	(Lee et al., 2009)
MANSUR	Different outcomes are reported	(Lee et al., 2020)
LEONARDI	Meeting abstracts	(Leonardi et al., 2017)
MOLA	Deferent design	(Martin-Mola et al., 2010)
MENTER	Different outcomes are reported	(Menter et al., 2010)
PAPP	Meeting abstracts	(Papp et al., 2014b)
PAPP	Meeting abstracts	(Papp et al., 2016b)
PARK	Different outcomes are reported	(Park et al., 2017)
PUIG	Different outcomes are reported	(Puig et al., 2014)
RAU	Different outcomes are reported	(Rau et al., 2004)
SCHREIBER	Different outcomes are reported	(Schreiber et al., 2005)
SEO	Cohort design	(Seo et al., 2005)
STROBER	Meeting abstracts	(Strober et al., 2016)
J-RAPID	Used same drug in both arms	(Tanaka et al., 2014)
TER WEE	Used same drug in both arms	(ter Wee et al., 2015)
THACI	Meeting abstracts	(Thaci et al., 2016)
TREMOULET	Follow-up less than 12 weeks	(Tremoulet et al., 2014)
TYRING	Meeting abstracts	(Tyring et al., 2009)
TEMPO TRIAL	Different outcomes are reported	(van der Heijde et al., 2006)
ATLAS TRIAL	Different outcomes are reported	(Van der Heijde et al., 2009)
SWEFOT TRIAL	Different medications	(van Vollenhoven et al., 2012)

WANG	Follow-up less than 12 weeks	(Wang et al., 2018)
WASCHER	Different outcomes are reported	(Wascher et al., 2009)
WEI	Used same drug in both arms	(Wei et al., 2020)
WESTHOVENS	Different outcomes are reported	(Westhovens et al., 2006)
PLANETRA	Used same drug in both arms	(Yoo et al., 2013)
ZEIN	Different medications	(Zein and Group, 2005)
ZOUBOULIS,	Meeting abstracts	(Zouboulis et al., 2018)
IL-17		
IAIN	Meeting abstracts reported with incomplete results	(McInnes et al., 2019)
GERDES	Different outcomes are reported	(Gerdes et al., 2020a)
PINTER	Different outcomes are reported	(Gerdes et al., 2020b)
KOERBER	Used same drug in both arms	(Koerber et al., 2018)
PAPAVASSILIS	Used same drug in both arms	(Körber et al., 2018)
SCULPTURE	Cohort design	(Mrowietz et al., 2015)
OELKE	Meeting abstracts	(Oelke et al., 2017)
OKUBO	Used same drug in both arms	(Okubo et al., 2019)
EMERY	Conference paper	(Emery et al., 2012)
MEASURE	Meeting abstracts	(Marzo-Ortega et al., 2020)
PAPP	Meeting abstracts	(Papp et al., 2016a)
RESZKE	Review	(Reszke and Szepietowski, 2017)
FIXTURE	Meeting abstracts	(Thaci et al., 2016)
Anti-6		
KENNEDY	Single arm design	(Kennedy et al., 2014)
TUCKWELL	Meeting abstract with incomplete results	(Tuckwell et al., 2015)
GILES	Meeting abstract	(Giles, 2016)
HEISSIGEROVA	Different outcomes were reported (ocular hypertension)	(Heissigerová et al., 2019)
TOPIRA	Different outcomes were reported	(van der Leeuw et al., 2020)
OHSUGI	Paper evaluation	(Ohsugi, 2008)
KOSTINA	Poster presentation	(Kostina and Lyskina, 2015)
WELLS	Used same drug in both arms of the study	(Wells et al., 2019)
YOKOTA	Different research design	(Yokota et al., 2014)
VAN RHEE	Single arm design	(Van Rhee et al., 2015)
KURZROCK	Different design (cohort study)	(Kurzrock et al., 2013)
ROSSI	Different design (cohort study)	(Rossi et al., 2010)
FREEMAN	Transcription of an oral presentation with incomplete results	(Freeman et al., 2015)

OGATA	Used same drug in both arms of the study	(Ogata et al., 2014)
PAPPAS	Meeting abstract	(Pappas et al., 2011)
MOLLAN	Review article	(Mollan et al., 2018)
QUARTUCCIO	Different design (cohort study)	(Quartuccio et al., 2020)
THOMAS	Non-randomised trial	(Thomas et al., 2012)
EL JAMMAL	Review article	(El Jammal et al., 2020)
AIZAWA	Different research design	(Aizawa et al., 2017)
CASAS	Meeting abstract	(Dom-Nguez-Casas et al., 2017)
WOODMAN	Different research design	(Woodman et al., 2017a)
DHILON	Review article	(Oldfield et al., 2009)
ROSWITCH	Different research design	(Darloy et al., 2019)
RUEDA	Review article	(Rueda et al., 2011)
SCHIRMER	Review article	(Schirmer et al., 2018)
KUME	Used the same drug in both arms of the study	(Kume et al., 2011)
IKONOMIDIS	Different outcomes were reported	(Ikonomidis et al., 2008)
AMANO	Abstract	(Amano et al., 2018)
MORI	Meeting abstract	(Mori, 2014)
FRAMPTON	Review article	(Frampton, 2013)
Purine and Pyrimidine synthesis inhibitors		
Kumar	Non-Randomised	(Kumar *et al.*, 2008)
Contreras	Different outcomes are reported	(Contreras *et al.*, 2009)
Bakker	Different outcomes are reported	(Bakker *et al.*, 2003)
Beckebaum	Different outcomes are reported	(Beckebaum *et al.*, 2009)
Brinker	Different outcomes are reported	(Brinker *et al.*, 1990)
Chapman	Used same drug in both arms	(Chapman *et al.*, 1987)
CAESAR	Different medications	(Ekberg *et al.*, 2007)
Schwartz	Different outcomes are reported	(Schwartz *et al.*, 2012)
Fisher	Used same drug in both arms	(Fisher *et al.*, 1998)
Forsythe	Different outcomes are reported	(Forsythe *et al.*, 1999)
Fujinaga	Different outcomes are reported	(Fujinaga *et al.*, 2008)
Galiatsou	Deferent design	(Galiatsou *et al.*, 2000)
Gheith	Used same drug in both arms	(Gheith *et al.*, 2011)
Gipson	Children	(Gipson *et al.*, 2011)
Hayati	Different outcomes are reported	(Hayati *et al.*, 2019)
Heckmann	Non-Randomised	(Heckmann *et al.*, 2011)
Hernandez	Used same drug in both arms	(Hernandez *et al.*, 2007)
Hilbrands	Different outcomes are reported	(Hilbrands *et al.*, 1996)
Hocker	Used same drug in both arms	(Hocker *et al.*, 2009)
Weber	Used same drug in both arms	(Weber *et al.*, 2010)

Hocker,	Children	(Hocker, *et al.*, 2019)
Ishaq	Deferent design	(Ishaq *et al.*, 2019)
Kalden	Used same drug in both arms	(Kalden *et al.*, 2003)
Kaltwasser	Deferent design	(Kaltwasser *et al.*, 2005)
Kobashigawa	Different medications	(Kobashigawa *et al.*, 2006)
Langone	Different outcomes are reported	(Langone *et al.*, 2011)
Langrehr	Different outcomes are reported	(Langrehr *et al.*, 1998)
Lee	Different medications	(Lee *et al.*, 2010)
Legendre	Used same drug in both arms	(Legendre *et al.*, 2003)
Maes	Patients used antihypertensive	(Maes *et al.*, 2004)
Manousou	Different medications	(Manousou *et al.*, 2014)
Samonakis	Abstract	(Samonakis *et al.*, 2013)
Mohammadi	Different medications	(Mohammadi *et al.*, 2017)
Mok, C. C.	Abstract	(Mok, C. C. *et al.*, 2020)
Ying	Deferent design	(Ying *et al.*, 2010)
Mourer	Used same drug in both arms	(Mourer *et al.*, 2012)
Mourer	Different outcomes are reported	(Mourer *et al.*, 2012)
Nakache	Different medications	(Nakache *et al.*, 2005)
Nematalla	Used same drug in both arms	(Nematalla *et al.*, 2007)
Otto	Different outcomes are reported	(Otto *et al.*, 1998)
Pelletier	Deferent design	(Pelletier *et al.*, 2006)
Poor	Used same drug in both arms	(Poor *et al.*, 2004)
Rathinam	Different outcomes are reported	(Rathinam *et al.*, 2014)
Rathinam	Different outcomes are reported	(Rathinam *et al.*, 2019)
Vera	Deferent design	(Vera *et al.*, 2018)
Rostaing	Different medications	(Rostaing *et al.*, 2013)
Sadek	Used same drug in both arms	(Sadeki *et al.*, 2002)
Saliba	Used same drug in both arms	(Saliba *et al.*, 2016)
Schnuelle	Deferent design	(Schnuelle *et al.*, 2002)
Stegall	Used same drug in both arms	(Stegall *et al.*, 1997)
Plassmann	Used same drug in both arms	(Plassmann *et al.*, 2012)
Sutherland	Used same drug in both arms	(Sutherland, 1985)
Traitanon	Different outcomes are reported	(Traitanon, 2019)
Wlodarczyk	Used same drug in both arms	(Wlodarczyk *et al.*, 2012)

Wolfhagen	Different outcomes are reported	(Wolfhagen *et al.*, 1998)
Wu, J.	Different medications	(Wu, J. *et al.*, 2020)
Zhang	Used same drug in both arms	(Zhang *et al.*, 2019)
Anti-IL1B		
Brucato	Different outcomes are reported.	(Brucato et al., 2015)
Buckley	Deferent design.	(Buckley et al., 2018)
Fleischmann	Different outcomes are reported.	(Fleischmann, 2003)
Krause	Meeting abstracts.	(Krause et al., 2015)
Popovic	Different outcomes are reported.	(Popovic et al., 2020)
Schlesinger	Meeting abstracts.	(Schlesinger et al., 2013)
Sunkureddi	Meeting abstracts.	(Sunkureddi et al., 2013)
Tesser	Different outcomes are reported.	(Tesser et al., 2004)
Asseldonk	Different outcomes are reported.	(van Asseldonk et al., 2011)
Wu	Deferent design.	(Wu et al., 2018)
Colchicine		
Albillos	Different outcomes are reported	(Albillos et al., 2013)
Bardin	Abstract	(Bardin et al., 2012)
Battezzati	Different outcomes are reported	(Battezzati et al., 2001)
Becker	Abstract	(Becker et al., 2013)
Bessissow	Different outcomes are reported	(Agzarian et al., 2018)
COVERT-MI	Different outcomes are reported	(Bresson et al., 2021)
Brucato	Abstract	(Brucato et al., 2015)
Deftereos	Different outcomes are reported	(Deftereos et al., 2014)
Levine	Different outcomes are reported	(Demidowich et al., 2020)
Demidowich	Different outcomes are reported	(Demidowich et al., 2019a)
Wolska	Different outcomes are reported	(Demidowich et al., 2019b)
Furst	Different outcomes are reported	(Furst et al., 2001)
AGREE study	Different design	(Furst et al., 2010)
Kaur	Different outcomes are reported	(Kaur et al., 2009)
Krishnan	Different design	(Krishnan et al., 2010)
Leung	Abstract	(Leung et al., 2010)
Bonis	Different outcomes are reported	(Leung et al., 2010)

Schlesinger	Abstract	(Schlesinger et al., 2013)
Alten	Different outcomes are reported	(Schlesinger et al., 2012)
Wu	Review	(Wu et al., 2018)
Zarpelon	Different outcomes are reported	(Zarpelon et al., 2016)

3.2.2 Description of included studies

The guidelines from the PRIMSA-P document were followed, which led to 141 RCTs, including 60,580 subjects and comprising the study of either a placebo or active pharmaceutical agents, being designated as meeting the criteria for inclusion in this review. In 75 of these studies, 31,545 (52.4%) participants were randomized to receive immunosuppressive therapies compared to placebo. Of these, 780 demonstrated an increased risk of hypertension onset. In 66 RCTs, 29,695 (47.6%) participants were designated to receive either an immunosuppressive therapies compared to active drugs, and the likelihood of hypertension was noted to be 2,387. A table of the features of the studies included in the review is presented in **Appendix B**. Data relating to the methodological design, the entry clinical history, the immunosuppressive treatment background prior to randomisation, pre-determined endpoints, the source and form of apposite endpoints, and preparations used for comparative purposes, were utilised as descriptors.

3.2.2.1 Entry clinical history

Subjects with high blood pressure at entry were included in 10 studies (Jover; Solomon; Giles; Rose; Gheith; Kahan; Simone; Takasahi; Choudhury; Sheng). Participants who had particular comorbidities at the initial assessment were recruited into all the studies. In 8 trials, the most frequently recognised pre-existing condition was diabetes (Jover; Solomon; Najarian; Sundel; Takasahi; Vitko; Yunyun; Choudhury), of which 5 were in the category relating to inhibitors of purine and pyrimidine synthesis. Solomon and Choudhury described elevated lipid levels as the principal comorbidity in their populations; a history of cardiovascular disease was described by Giles and Sheng.

3.2.2.2 Immunosuppressive treatments

Seven class types of immunosuppressive therapies were evident, all of which were considered likely to have an association with hypertension risk. These comprised methotrexate, and inhibitors of tumour necrosis factor (TNF), anti-interleukin-17 , anti-interleukin-6, anti-interleukin-1B, purine and pyrimidine (including leflunomide, mycophenolate and azathioprine) and colchicine.

3.2.2.3 Active comparators

A range of anti-inflammatory therapies were employed as active comparative agents in 7 group trials; these included anti-inflammatory medications, e.g. prednisone, disease-modifying anti-rheumatic drugs, TNF inhibitors and other biological agents.

3.3 Bias risk in included studies

The bias risk appraisal method utilised for all the included studies is presented in **Chapter 2,Section 2.1.6**. In keeping with the inclusion criteria (See **Appendix C 'Methodological quality of included studies'**), all the studies took the form of a RCT. A summary of the bias risk (%) for each study encompassed in the review is illustrated in **Figure 3-1**. A further potential cause of bias is the funding source for each study.

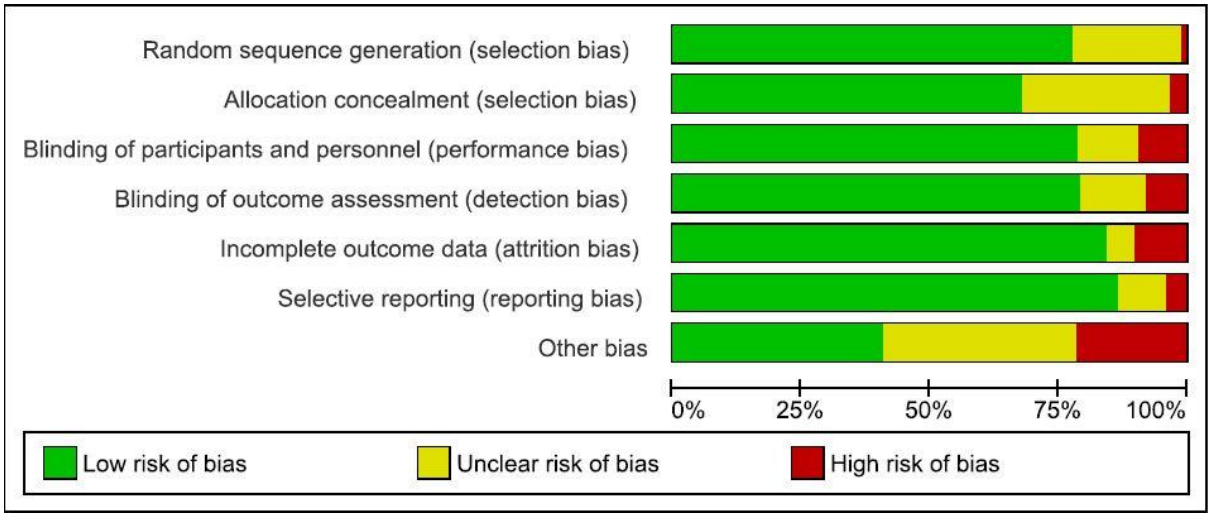

Figure 3-2 Risk of bias graph for the studies included in the review, which indicates the evaluations made in each paper relating to the bias risk for each item expressed as a percentage.

3.3.1 Randomisation and allocation

In 97 (78.6%) of the included RCTs, the method relating to generation of the random sequencing was appropriately documented. 26 studies were noted to have an unclear risk of bias for this item due to a lack of relevant data. (Ambitoin; Burmester; Certain; Irie; De Groot; Der Veen; Desmopaz; Drosos; Keystone; Edwards; Emery; Ferraccioli; Keystone; Le Loet; Lithe; Monarch; Naeini; Nasonov; Option; Pakfetrat; Rosesirround-H, 2017; Sirround-H, 2018; Takeuchi; Terkeitaub; Toward; Visara). Lack of adequacy with respect to the way in which the report was produced gave rise to a high bias risk in the study published by Jover.

85 (68.7%) trials were deemed to have a low bias risk in relation to concealing allocation. In this respect, the bias risk in 36 studies was not transparent, as the method utilised was not documented (Ambitoin; Becker; Beissert; Bijlama; Bijlsma; Burmester; Der Veen; Edwards; Emery 2000; Fasscinate; Ferraccioli; Gheith; Giles; Kakahasi; Karanikolas; Keystone; Le Loet; Lithe; Metzler; Monarch; Najarian; Nasonov; Option; Rose; Simone; Sirroind-T; Sirround-H, 2017; Sirround-H, 2018; Solomon; Takasashi; Takeuchi, 2020; Takeuchi, 2021; Tempo; Toward; Visara; Vitko). A high bias risk owing to the allocation concealment process being inapposite was recognised in 4 stuides (Boudjema; Ionannides; Sticherlins; Yunyun).

3.3.2 Blinding

Subjects and investigators were blinded with respect to the intervention or control (placebo or active) in 98 of the trials encompassed in the review, which were therefore judged as having a low performance bias risk. Open-label designs were associated with 12 studies, in which the bias risk in this regard was presumed to be high as both subjects and involved staff were not blinded to therapy allocations (Groot; Desmopaz; Drosos; Ferraccioli; Giles; Ioannides; Boudjema; Karleen; Marchesoni; Sticherlins; Yunyun; Visara). 15 studies were unclear on the risk of bias due to a lack of information on this process (Naeini; Becker; Beissert; Gheith;

Karanikolas; Keystone; Lithe; Metzler; Najarian; Simone; Solomon; Takasashi; Takeuchi; Toward; Vitko).

The blinding of the outcome assessment was thought to be acceptable in 75% of the included RCTs. Sixteen RCTs were judged to have an unclear risk of bias due to insufficient information (Becker; Beissert; Irie; Deer Veen; Keystone; Ferraccioli; Gheith; Karanikolas; Edward C Keystone; Lithe; Metzler; Naeini; Najarian; Rhee; Simone; Takeuchi). Ten trials exhibited a high bias risk in relation to blinding to the endpoint appraisal (Boudjema; De Groot; Giles; Ioannides; Karleen; Sticherlins; Takasashi; Visara; Vitko; Yunyun).

3.3.3 Incomplete outcome data

In 105 (90.5%) of the trials included in the review, the attrition bias was thought to be low owing to a number of factors. Firstly, loss to follow-up was between 0.01% and 17.2%, and failed to reach significance. Secondly, the loss rate was equivalent for all arms of the studies, and finally, intention-to-treat standards were applied to the analysis. As increased rates of follow-up attrition were evident in intervention versus control cohorts in 13 studies, and the rate of discontinuation in these studies was only described in the former rather than the latter group, the risk of attrition bias was judged to be high in these papers. Inadequate data to enable the bias risk to be determined were provided in 7 studies (Future; Keystone; Nasanov; Rhee; Schiff; Tahir; Tempo).

3.3.4 Selective reporting

All endpoints were documented in 93 (95.6%) of the studies encompassed in the review, in keeping with the described methods or research protocols. Lack of clarity relating to this aspect owing to the failure to provide information on the endpoints of the study or to include the relevant protocol was observed in 12 papers (Der Veen; Drosos; Future; Keystone; Nasonov; Option; Sirroind-T; Sirround-H, 2017; Sirround-H, 2018; Tahir; Toward; Visara). Reporting bias risk was deemed to be high in 5 RCTs (Becker; Combe; Papp; Schiff; Takeuchi).

3.3.5 Other potential sources of bias

3.3.5.1 Source of funding

It was considered that bias could arise as a result of study sponsorship; sources of funding were categorised as originating from profit, non-profit or mixed profit class institutions. Pharmaceutical enterprises offered funding to 63 trials; such sponsorship was provided as grants, materials for the study or personnel, e.g. to assist with authorship or statistical data analysis.

Forty RCTs received monies from non-profit enterprises, or partial funding from those that operated for profit. Autonomous academic non-profit institutions provided fiscal support for a further 22 studies. In RCTs where sponsors made no immediate contributions to study design, data gathering, analysis or interpretation, a low sponsorship bias risk was thought to be present, which applied to under half of the studies encompassed in the review. Where sponsors took on these roles in 27 studies, these actions resulted in a high level of sponsorship risk bias. This type of bias could not be determined in 48 studies.

3.3.6 Summary

Clinical investigations or interventional research must be conducted in such a manner so as to provide a thorough understanding of the efficacy, effectiveness and dangers associated with any new drug presented for the management of any clinical illness. In order to establish that improvement or deterioration is not random, the method of treatment must be contrasted with different paradigms of therapy or no intervention, i.e. active and placebo controls, respectively (Kahan et al., 2015) .

An investigation may be described as either open-labelled or blinded. Blinding techniques render the person taking part and/or evaluating physician unaware of the medical care received during the trial (Sil et al., 2019). Thus, any aspect of bias that may be introduced due to individual tastes or any arbitrary aspect of result evaluation, e.g. a tool, such as a doctor's worldwide rating to measure the result, can be avoided. This method has now been expanded to include data assessment by a statistician in order to ensure result accuracy. As a consequence,

blinding can enable the elimination of intentional or accidental bias, increase the impartiality of outcomes, and ensure the trustworthiness of study findings.

Attrition bias is a type of selection bias which is caused by systematic disparities in the quantity and manner in which research participants are lost (Nunan et al., 2018). Differences between individuals who withdraw from a study and those who stay, particularly amongst groups of participants, can be the cause of any apparent effect, rather than the intervention itself. Following the exclusion of studies which had a high or uncertain risk of attrition bias, associations between variables were no longer detectable.

Selective reporting can occur, for instance, when a researcher, journal editor or trial sponsor believes that negative data, i.e. when no impact of a new treatment is discovered, are boring or insignificant (Jefferson, 2020). However, disclosing negative outcomes contributes vital knowledge to the body of research and can prevent unneeded trials from being conducted. If clinical findings from studies were to guide choices about treatment in the medical field, patients as well as prescribers would have to be willing to depend on the study data offered to them.

In recent decades, the detection of sponsorship bias has harmed the trustworthiness of much of the supporting evidence foundation for a few of the most successful curative and preventative treatments. Sponsorship bias refers to the modification of medical research methodology as well as reporting in order to favour the sponsor's goals. The use of the term, ‘sponsor’, it is not meant to imply that the sources of bias are either simply or mostly economic. Sponsors include funders and participants involved in the design, setup, operation and documentation of clinical trials, as well as study team participants.

The risk bias assessment revealed that the risk in the majority of the evaluated studies assessed was either low or unclear. The latter scenario was mostly caused by the lack of additional details concerning the methodologies. Comparatively, some high risk evaluations resulted from either proportional imbalance or incomplete data presentation in the studies.

4. Association between Methotrexate and risk of hypertension

4.1 Introduction

4.1.1 Methotrexate

Various forms of immunosuppressants exist, but methotrexate belongs to a unique class of drugs that systematically slow down the body's immunity and, during the process, reduce bodily inflammation. Additionally, methotrexate can treat several types of cancer. As an antimetabolite crucial in immunosuppressants and chemotherapy, it also treats various neoplastic ailments. However, methotrexate cannot be combined with other drug classes because of the side effects it causes. Methotrexate should be considered a potent medication. How a patient takes the medication, and the prescribed dosage often depends on their treatment response and medical condition. Essentially, methotrexate is a disease-modifying antirheumatic drug (DMARD) often used to suppress immune system activity (Baghdadi, 2020). Notably, DMARDs are known to modify the underlying bodily diseases instead of treating the symptoms. The immune system protects the body from getting infections through inflammatory actions to fight them. The inflammation is known to cause specific side effects, such as heat, swelling, pain, and redness (Chen et al., 2018). However, in some conditions, the immune system can mistakenly attack body parts, like joints, and cause other illnesses. Usually, arthritis and related health conditions prompt doctors to prescribe methotrexate (Guo et al., 2018).

4.1.2 Mechanism action of Methotrexate

Similar to other drugs, methotrexate has a specific form of action. In most cases, as a drug that suppresses cancer and inflammation, methotrexate acts as an antifolate antimetabolite. Once in the human cells, it forms methotrexate-polyglutamate. The drug's absorption results in the inhibition of enzyme dihydrofolate reductase, an action that catalyses the conversion of dihydrofolate to tetrahydrofolate, which is an active form of folic acid. In the body's physiological functioning, tetrahydrofolate is vital to the synthesis of DNA and RNA nucleotides (Naunova-Timovska et al., 2020). Similarly, methotrexate-

polyglutamate inhibits the conversion of thymidylate synthase and purine, a process that undermines DNA synthesis.
Methotrexate's complex functions and reactions create a cytotoxic effect that suppresses cancers.

The cytotoxic properties of the drug attack rapidly multiplying cells during the S phase of the cell cycle, thereby impairing malignant growth while protecting normal tissues (Mahajan, 2019, Barreto et al., 2022).
Methotrexate's cytotoxicity results in thymidylate synthase and dihydrofolate reductase (DHFR) inhibition and an immediate alteration of folate transportation. The drug's ability to suppress lymphocyte multiplication makes it an effective immunosuppressant.
In managing autoimmune ailments, the drug utilises different mechanisms. However, the basic concept is the inhibition of the enzyme AICAR transformylase, a process that results in guanine and adenosine metabolism. The process leads to the repression of T-cell activation, the systematic down-regulation of B-cells, and further activation of CD-95 T-cell sensitivity. Other processes involved in managing autoimmune ailments include methyltransferase repression and inhibition of beta-1 binding (Kishi, 2020). The complexity involved in transforming methotrexate to manage autoimmune ailments also triggers the emergence of other diseases, including hypertension. Therefore, evaluating how methotrexate manages cancers and inflammation, in relation to hypertension, guides the present study. The fundamental issue of focusing on how the drug potentially triggers hypertension stems from its adverse side effects (Cui et al., 2022). Although the primary side effects presently noted include loss of appetite, nausea, vomiting, and mucosal ulcers, further research on other corresponding ailments is central to present and future studies.
As aforementioned, methotrexate is known to have immunosuppressive properties. The mechanism is thought to inhibit lymphocyte multiplication. However, Škorić et al. (2020) noted that the mechanism for methotrexate is still not well explored when managing rheumatoid arthritis. Singh et al. (2017) claimed that the suggested mechanisms of action include anti-inflammatory or immunosuppressive effects or both. For instance, in psoriasis, the production rate of the epithelial cells is often significantly increased compared to normal skin.

Shah et al. (2021) added that the differential in the proliferation rate is the core issue for using methotrexate to manage the psoriatic process. When understanding the pharmacokinetics of methotrexate, the absorption model must be understood. According to Mazouyès et al. (2017), methotrexate is often absorbed completely after parenteral administration, and peak serum concentration happens between thirty and sixty minutes after intramuscular injection. Notably, methotrexate is often distributed among various body tissues, especially in the spleen, liver, kidneys, gallbladder, and skin. The mechanism of action of methotrexate is illustrated in the figure below.

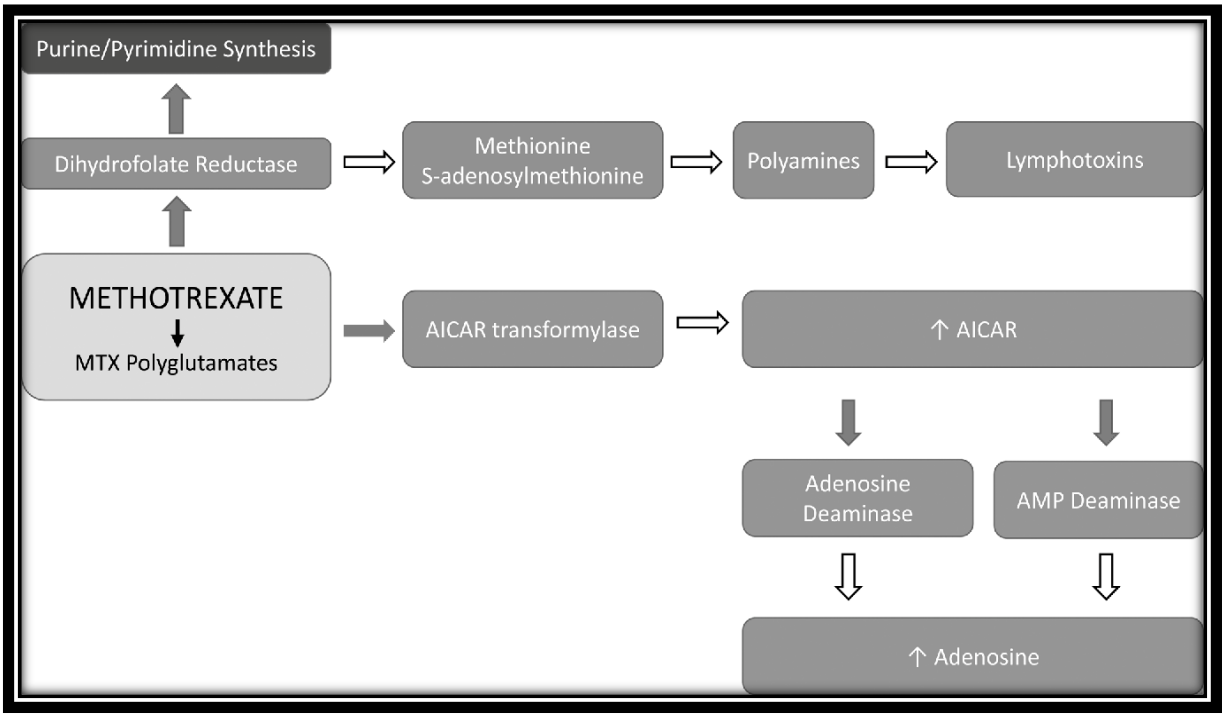

Figure 4-1 The mechanism action of methotrexate

Adapted from (Chan, 2013).

In **Figure 4-1**, MTX acts as an antirheumatic drug that inhibits enzyme dihydrofolate reductase production, a process that impedes purine/pyrimidine synthesis. This process leads to reduced tetrahydrofolate, which, in turn, inhibits DNA synthesis and pyrimidines and purine production. Therefore, this explains why the side effects of MTX include bone marrow suppression and stomatitis (Chan, 2013). The general process of undermining tetrahydrofolate production leads to the production of S-adenosylmethionine, methionine and polyamines. This process results in the over-accumulation of these compounds in the urine of patients with rheumatoid arthritis. MTX works by suppressing polyamines in lymphocytes. Once

consumed, MTX relies on MTX polyglutamates derived mainly from 7-hydroxymethotrexate found in the liver and adipose tissues. The drug takes a relatively prolonged time to act based on the slow effect of its anti-inflammatory action. Methotrexate polyglutamates, compounds formed after MTX is consumed, act as aminoimidazole carboxamide ribonucleotide (AICAR) transformylase inhibitors (Chan, 2013). AICAR accumulation triggers adenosine deaminase and AMP deaminase inhibition. Limiting the catabolism of adenine and adenosine nucleotides and adenosine regulates the dephosphorylation of AMP.

4.1.3 Methotrexate-linked reduction of inflammation

Methotrexate is known for its anti-inflammatory properties, which are effective even in a low dosage, as observed on the synovial tissue of patients with rheumatoid arthritis (Emre et al., 2018, Hoffman et al., 2019).

Jang et al. (2021) added that methotrexate reduces monocytic cell growth and increases their apoptosis. Moreover, the drug comprises folic acid containing anti-proliferative, cytotoxic, and anti-inflammatory properties used to treat cutaneous disorders, including keratoacanthoma, dermatitis, sclerosis and lupus erythematosus (Nedelcu et al., 2019). These properties explain why the drug is ideal for preventing different inflammation forms.Kim et al. (2019) noted that methotrexate causes indirect inhibitory impacts through cytokine modulation on synovial metalloproteinase production, triggering their inhibitors. The overall structure of the anti-inflammatory effects is illustrated in the figure below.

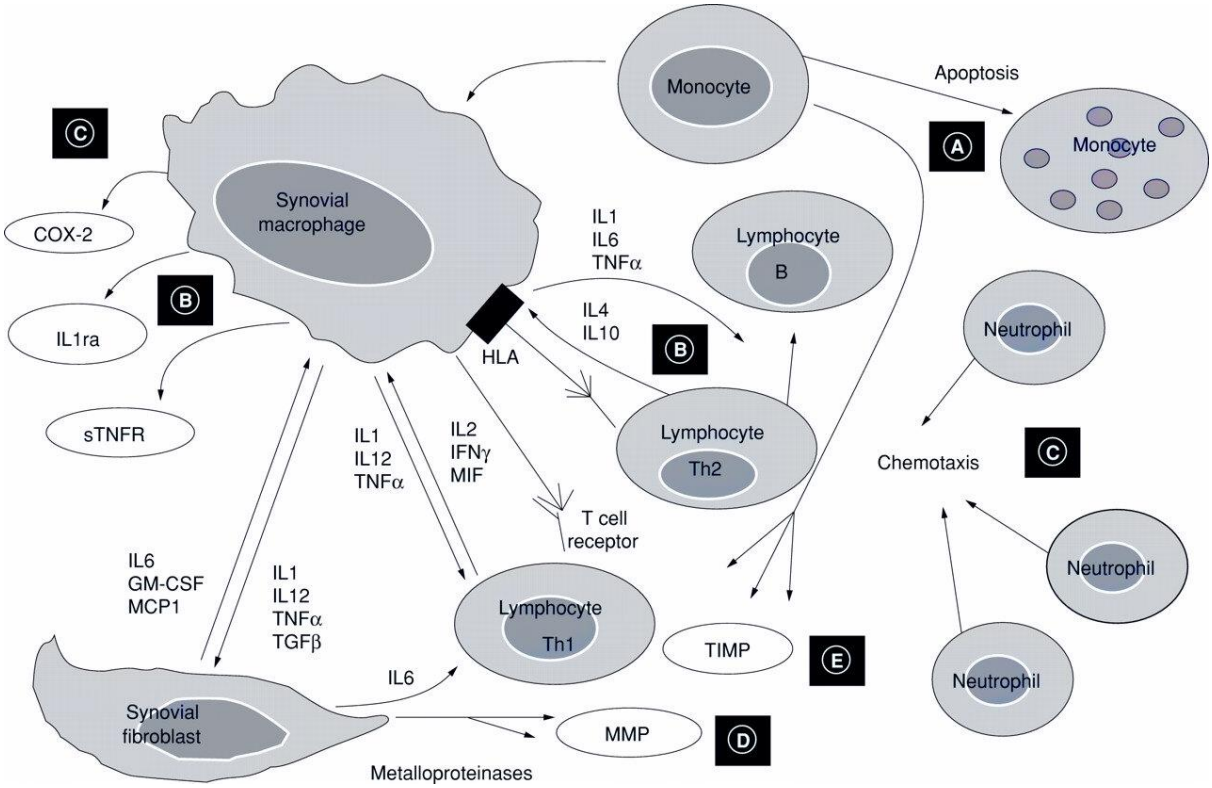

Figure 4-2 Methotrexate-linked reduction of the joint inflammation process

Adapted from (Cutolo et al., 2001).

Figure 4-2 illustrates how MTX reduces the inflammation process. Contextually, low MTX doses in the synovial tissues in section A significantly reduce monocytic cell growth, a process that increases cell apoptosis. In section B, MTX triggers IL6 and IL1 but also leads to increased production of IL-1ra. Similarly, MTX triggers IL10 and IL4 gene expression, a process that also undermines gene expression for Th1 cytokines. In section C, MTX inhibits COX-2 synthesis as well as neutrophil chemotaxis. Conversely, MTX creates an inhibitory effect through cytokine modulation on synovial metalloproteinase (MMP), resulting in the stimulation of their inhibitors (TIMP), as expressed in section E.

4.1.4 Rationale behind the current study

Numerous studies have been conducted to determine how methotrexate affects blood pressure. Therefore, to definitively evaluate the link between methotrexate and the risk of hypertension, it is helpful to consider the existing works on the topic.

Thus, reviewing theories that best explain the subject matter is ideal in drawing well-informed inferences. A study by He et al. (2021) on the link between arterial stiffening and methotrexate treatment found that there could be a theoretical relationship between the two. However, it depended on a person's age and other related demographic and clinical factors. The rationale behind the theoretical findings in Hadwen et al. (2021a)'s research is based on the fact that the drug affects the cell inflammation process and arterial stiffness. However, while the arterial stiffness and cell inflammation management process could potentially affect blood pressure levels, the investigation found that patients using methotrexate in managing various ailments recorded minimal blood pressure level changes. Mangoni et al. (2017a) in their study of how methotrexate affected blood pressure in patients with rheumatoid arthritis, found that the drug created arterial stiffness, significantly lowering patient blood pressure. Moreover, these patients had healthier blood vessels as the drug created a salutary effect on veins and arteries, which reduced the potential risk of stroke and heart attack. Such findings were consistent with Mangoni et al. (2017a), which adopted the UA-767PC theory and found that while working effectively on the body's immunity, methotrexate demonstrated a significant reduction in both systolic and diastolic blood pressure and also PWV, which is a marker of arterial stiffness.

4.2 Methodology

4.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis have been described in **Chapter 2 (Methodology for all groups).**

4.2.2 Data extraction

The initial search yielded 1,186 articles using the search strategies detailed in the Appendix A, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of the research (see **Figure 4-3**). After removing duplication, the remaining 712 citations or abstracts were assessed for inclusion criteria. At that point, 591 articles were eliminated based on a title and abstract review process, almost 83% of the total, as predefined by the PICOS criterion. Of the 121 publications that remained for eligibility studies, ninety-five were eliminated after a full-text screening for several reasons which are described in **chapter 3,Table 3-1**. Ultimately, twenty-six trials with 11,265 patients enrolled for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

4.2.3 Description of excluded studies

A total of ninety-five publications were excluded after an extensive eligibility check of their full text. Four trials (Popovic, Cirt, Sandhu and Vanni) reported different outcomes, which did not mention hypertension (HTN). One study (Marguerie) had a follow-up period under three months; hypertension is known to show clearly after three months. Three studies (Burmester, Kremer and Woodman) were removed for having a different display, which was the Cohort type in all cases.

Two studies (Dunsmore and Ringden) were excluded because, in one, the participants were children and the other mixed adults with children, which would render this study's results inaccurate.

Three studies (Murata, Option and Rueda) were reviews. The most excluded type of studies were those who had used MTX in both arms, abstracts, annual meetings,

and conferences. **Chapter 3,Table 3-1** summarises the reasons for the elimination of each trial.

4.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.

Sensitivity analyses were completed by the exclusion of trials with [1] poor methodological qualities; [2] small sample sizes with less than 100 total participants; and [3] studies not crossing Cl 95%.

Subgroup analyses for MTX were performed as follows: (1) comparator drugs; (2) clinical setting; (3) duration of follow-up.

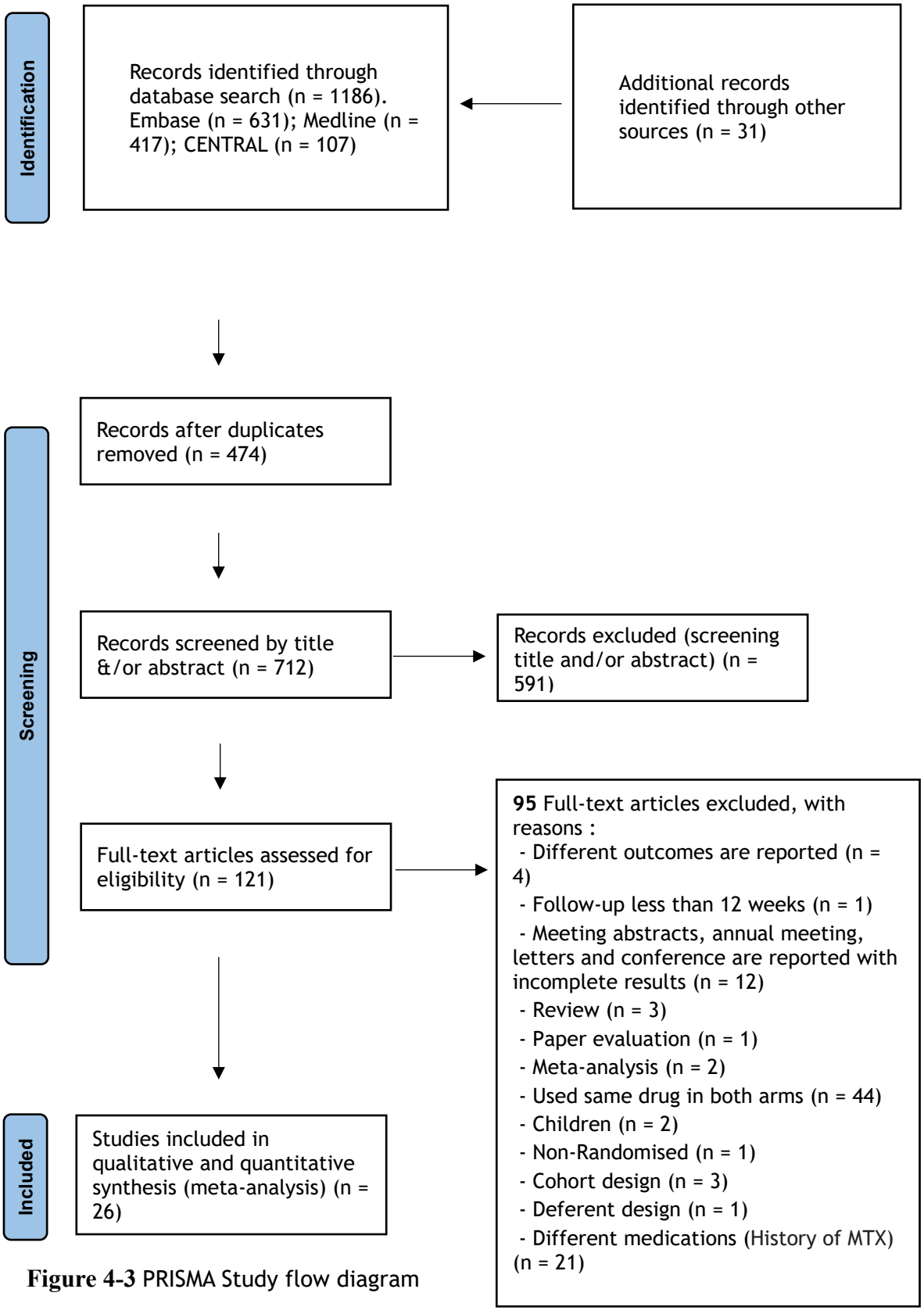

Figure 4-3 PRISMA Study flow diagram

4.3 Results

In total, twenty-six eligible MTX trials with 11,265 patients were enrolled, with an average follow-up period of 1.5 years (range four months to five years).
The average patient age for all trials was fifty-eight years old.
The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

Figure 4-3 provides a summary of the trial searching and identification process. Ninety-five studies were excluded for logical reasons.
Table 3-1 in chapter 3, records the reasons for the excluded studies and twenty-six RCTs (randomised controlled trials) were used for the final review.

The majority of studies were published since 2000.However, there is one study (Claude Irie), published in 1985. It compared MTX with CSP; fifty-six patients with leukaemia received marrow transplants and reported hypertension and other conditions as incidence.

Some studies were published in the nineteen-nineties such as Der Veen, Strand and Drosos. Der Veen's study, published in 1996, investigated the effect of MTX in the treatment of gain cell arteritis and polymyalgia, and reported a number of patients experiencing adverse effects, one of them hypertension. Strand's study, published in 1999, compared three arms, one of them treated with MTX so it was placed in the Placebo and Active drugs subgroups. The Drosos report was published in 1998 with rheumatoid arthritis patients treated with CS and MTX. Two studies (J. Barker and Takeuchi) were never published.

Only five studies compared MTX with a placebo (Coparali, Der Veen, Jover, Solomon and Strand); all of them reported hypertension as an adverse event.
The majority of included RTCs compared MTX to active controls involving cyclosporine, anti-TNF, leflunomide, rituximab, cyclophosphamide, azathioprine, CH1504, sulfasalazine, rapamycin, pazopanib and anti-IL6. Some of these were divided into subgroups (See Figure 7-2) and others were not because each drug had only one study which cannot be used for the purposes of meta-analysis.
Desmopaz used a combination therapy in one arm, where MTX was combined with vinblastine.

Ferraccioli divided patients into three groups, giving monotherapy only in the first six months; afterwards, a combination of drugs was employed. The Keystone study divided patients into four treatment groups in which two arms were treated with monotherapy and the other two with a combination. Marchesoni's trial period was twenty-four months; the first six months combined CSA with MTX. Afterwards, the treatments were separated, each one in an independent arm.
Tempo employed a study period of two years; in the first year, patients were treated with either etanercept or MTX and then a combination therapy of etanercept and MTX in the second year.

Most of the studies employed a double-blind design except for six (Desmopaz, Drosos, Ferraccioli, J. Barker, Le Loet and Metzler) who used an open-label design. Three studies (Claude Irie, De Groot and Naeini) did not specify the nature of the design, whether it be open or double-blind. None of the studies implemented a factorial design.

The follow-up study periods were at least three months and the most extended was five years. All the study participants were adults with a mean age of over fifty years old. All participants in the studies were male and female but differ in proportion from study to study. The Claude Irie report, published in the nineteen-eighties did not specify the sex of the participants, perhaps due to insufficient information.

In most studies, the patients have been diagnosed with autoimmune diseases such as rheumatoid arthritis, except in the Desmopaz report, in which patients were diagnosed with desmoid tumours. All the relevant details are described in **Table 4-1**.

Table 4-1 The underlying disease of each trial

Trial	Background disease	Trial	Background disease
Coporali	Polymyalgia rheumatica	Ferraccioli	Rheumatoid arthritis
Der Veen	Polymyalgia rheumatica and giant cell arteritis	Ishaq	Rheumatoid arthritis
Jover	Giant-cell arteritis	J. Barker	Plaque psoriasis
Solomon	Cardiovascular inflammation	Karleen	Systemic sclerosis
Strans	Rheumatoid arthritis	Keystone	Rheumatoid arthritis
Ambitoin	Rheumatoid arthritis	Le Loet	Rheumatoid arthritis
Bijlama		Marchesoni	Rheumatoid arthritis
Claude Irie	Marrow transplantation for Leukemia	Metzler	Wegener's granulomatosis
De Groot	Antineutrophil cytoplasmic Antibody-Associated Vasculitis	Naeini	Lichen planopilaris
Desmopaz	Desmoid tumours	Strand	Rheumatoid arthritis
Drosos	Rheumatoid arthritis	Takeuchi	Rheumatoid arthritis
Edward C Keystone	Rheumatoid arthritis	Tempo	Rheumatoid arthritis
Edwards	Rheumatoid arthritis	Emery	Rheumatoid arthritis

A total of 5240 patients from five studies compared MTX to a placebo and were included in the meta-analysis. MTX was compared to other active drugs in twenty-one studies which included a total of 6066 patients. When MTX was compared to the placebo, there was no significant difference in the risk of hypertension between MTX and the placebo (RR = 0.93, 95% CI, 0.61; 1.44, P = 0.75). A total of thirty-three and thirty-two events occurred in MTX and the control groups, respectively. Low and non-statistically significant heterogeneity was observed between studies (I2 = 14%, P = 0.33), indicating that the variability in the observed effect sizes between studies can be attributed to chance. The highest weight was recorded by the Jover study (54.0%).

When MTX was compared to other active drugs, a statistically significant difference was observed in the risk of hypertension between groups (RR = 0.47, 95% CI, 0.34; 0.65, P = 0.00001) favoring the MTX drug. A total of ninety-two and two hundred eleven events occurred in MTX and the active drug groups, respectively. The effect size could not be estimated in one of the studies because no events occurred in either arm. The effect size was statistically significant in

six studies, all of which favored the MTX drug. The highest weights were assigned to studies Ferraccioli, Le Loet and Tempo. Low heterogeneity was observed between studies (I^2 = 29%, P = 0.11) **(**see **Figure 4.4)**

Results did not change when the fixed effects model was used for the analysis. The risk of hypertension was not significantly different between MTX and the placebo groups (RR = 0.96, 95% CI, 0.65; 1.41, P = 0.83). The Jover study contributed to approximately half of the weight of the meta-analysis (48.1%). The effect size was not statistically significant in any of the studies. The risk of hypertension was lower in MTX compared to other active drugs and the effect size was similar to that produced by the random-effects model (RR = 0.43, 95% CI, 0.33; 0.54). The Emery and Tempo studies were assigned the highest weights (10.3% and 14.5%, respectively)**(**see **Figure 4-5).**

in Appendix D, Figure D-1, the represented funnel plot features a missing study in the middle left and bottom right-hand side of the plot. An outlier study can be seen outside the triangular region on the right-hand side, which was identified as the Ferraccioli study. It is likely that the asymmetry of this funnel can be attributed to selective outcome reporting bias when located studies may not provide usable data for the outcome of interest.

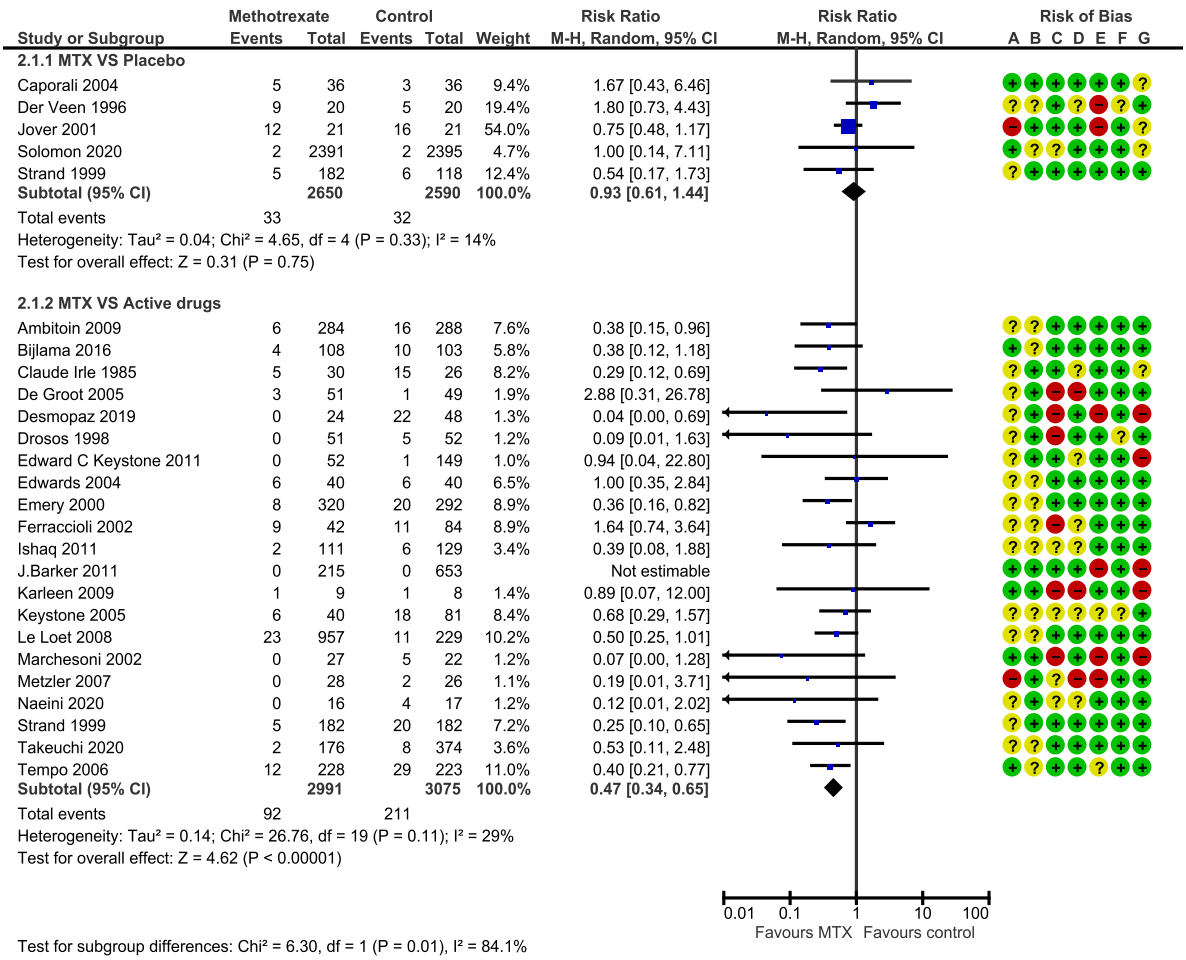

Figure 4-4 Random effects model for the association between MTX drug and the risk of hypertension.

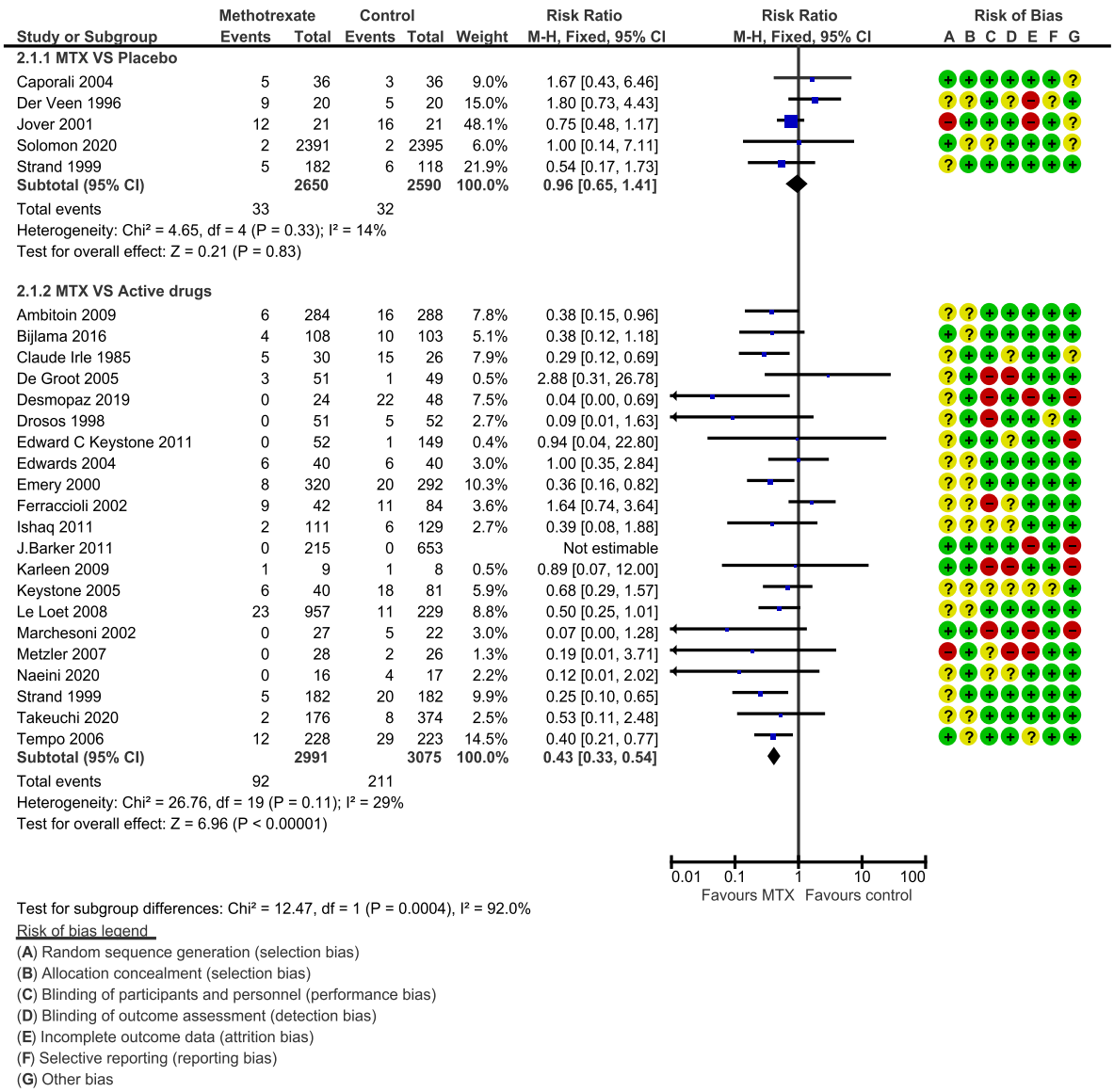

Figure 4-5 Fixed effects model for the association between MTX drug and the risk of hypertension.

4.3.1 Sensitivity analysis

Sensitivity analysis was performed to assess the robustness of estimates. The association between the use of methotrexate and the incidence of hypertension was evaluated after excluding (1) studies with a high risk of bias; (2) studies with a small sample size; and (3) studies not crossing 95% CI.

In Figure 4-6, the Der Veen and Jover studies with a high risk of bias were excluded in the placebo subgroup, while studies Desmopaz, Marchesoni, and Metzler were excluded in the active subgroup.

No association was observed between the use of methotrexate and the incidence of hypertension (RR = 0.89, 95% CI, 0.40; 2.00, P = 0.78), indicating that the risk of hypertension is not significantly different between methotrexate and the placebo arm. No heterogeneity was observed between studies (0%). The risk of hypertension was still lower in methotrexate than other drugs when high risk of bias studies were excluded (RR = 0.50, 95% CI, 0.37; 0.68, P = 0.00001). The heterogeneity between studies decreased to 28%. These results indicate that the estimates from the RE model are robust after excluding high RoB studies.

Three studies with small sample sizes were excluded in the placebo arm and twelve in the active subgroup arm. Similar estimates were obtained when methotrexate was compared to the placebo arm (RR = 0.63, 95% CI, 0.23; 1.73, P = 0.37), indicating that the risk of hypertension is not significantly different between methotrexate and the placebo arm. The risk of hypertension was still lower in methotrexate than in other active drugs when eleven studies with a small sample size were excluded (RR = 0.41, 95% CI, 0.3; 0.56, P = 0.00001). **(**see **Figure 4-7)**

Seven studies (Desmopaz, Emery, Le Loet, Tempo, Strand, Ambitoin and Claude Irie) were excluded from the active drug subgroup comparison, and fourteen were included in the analysis. After exclusion, the estimate from the RE model was not

statistically significant, although the estimate increased compared to the analysis, which included all studies (RR = 0.66, 95% CI, 0.40; 1.07, P = 0.09). A total of 33/996 and 78/1787 occurred in methotrexate and the comparator groups, respectively **(See Figure 4.8).**

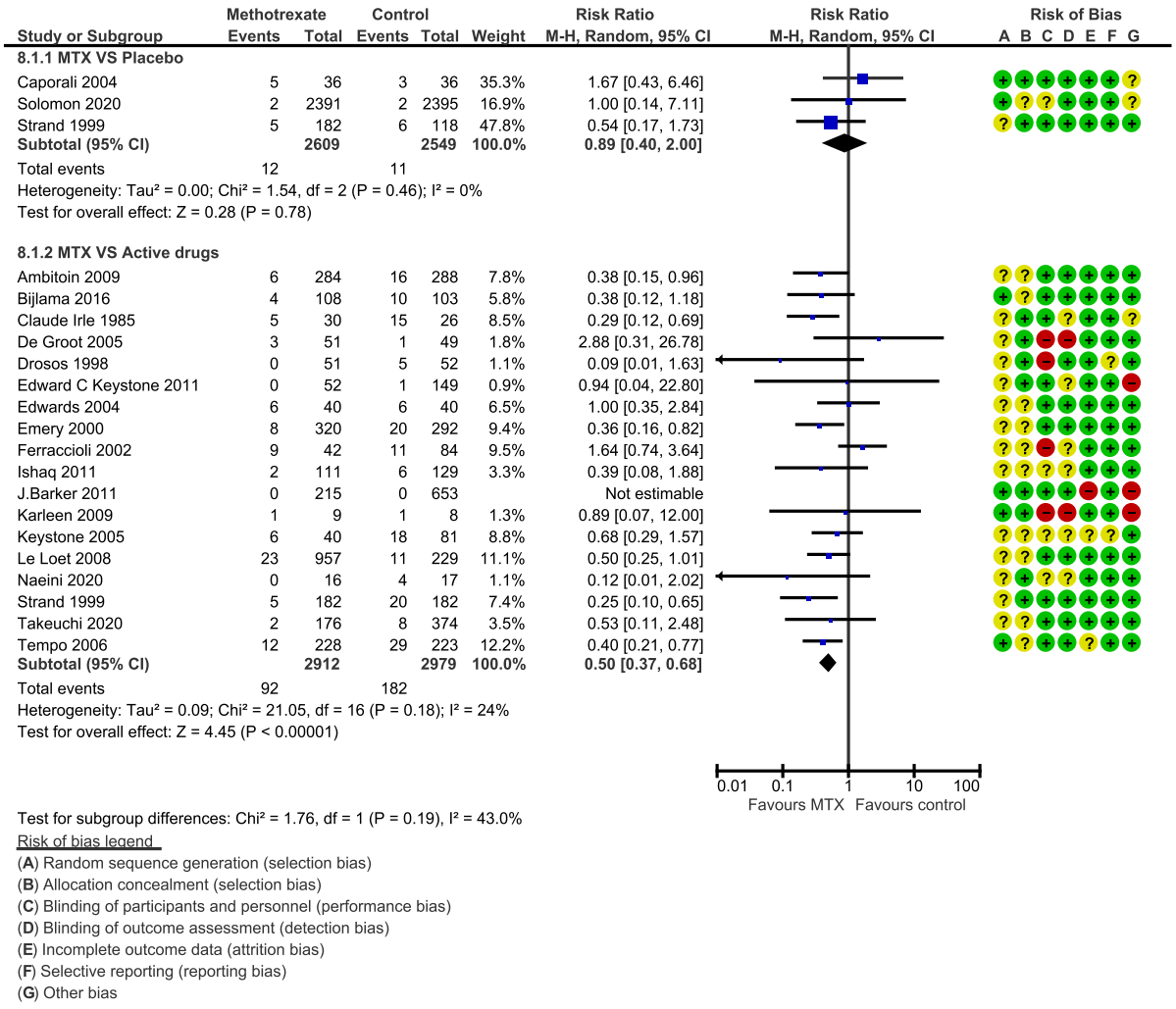

Figure 4-6 Sensitivity analysis for the association between the use of methotrexate and the risk of hypertension (RE model) after excluding studies with a high risk of bias (RoB).

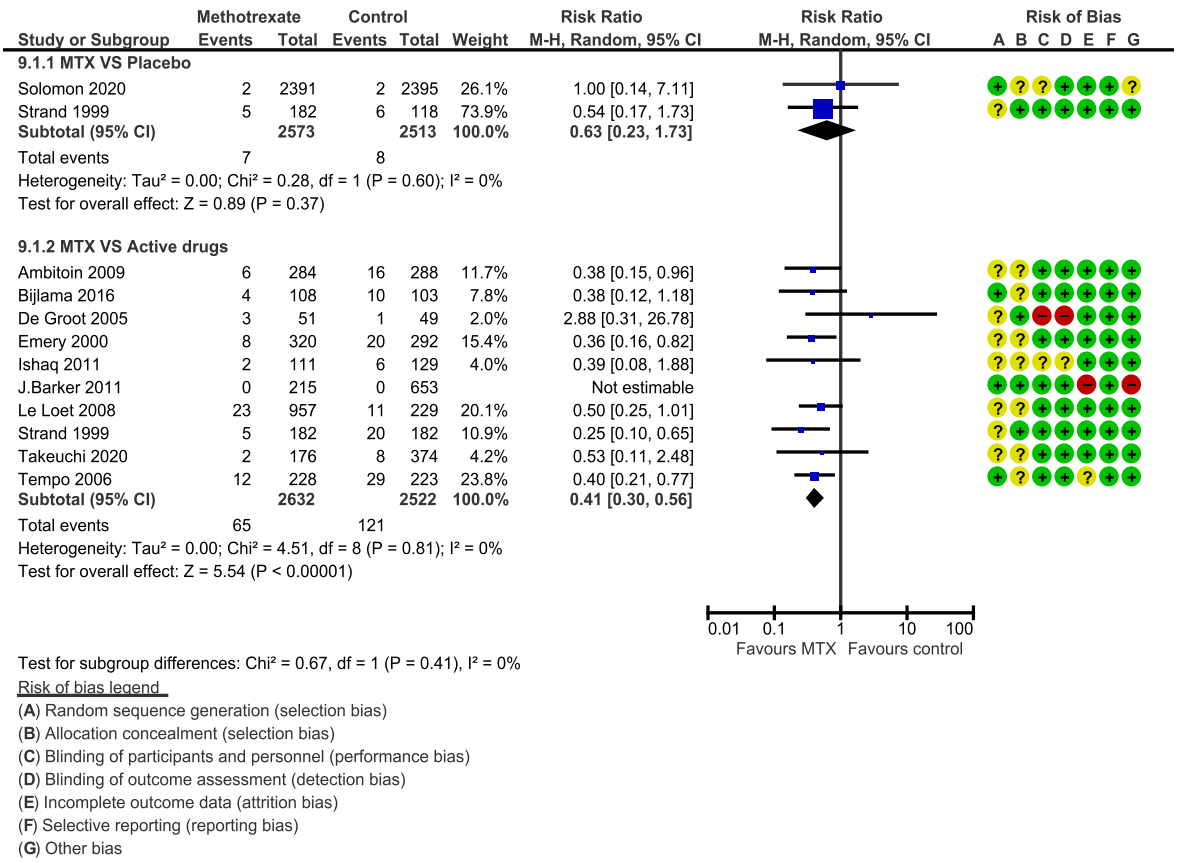

Figure 4-7 Sensitivity analysis for the association between the use of methotrexate and the risk of hypertension (RE model) after excluding studies with a low sample size.

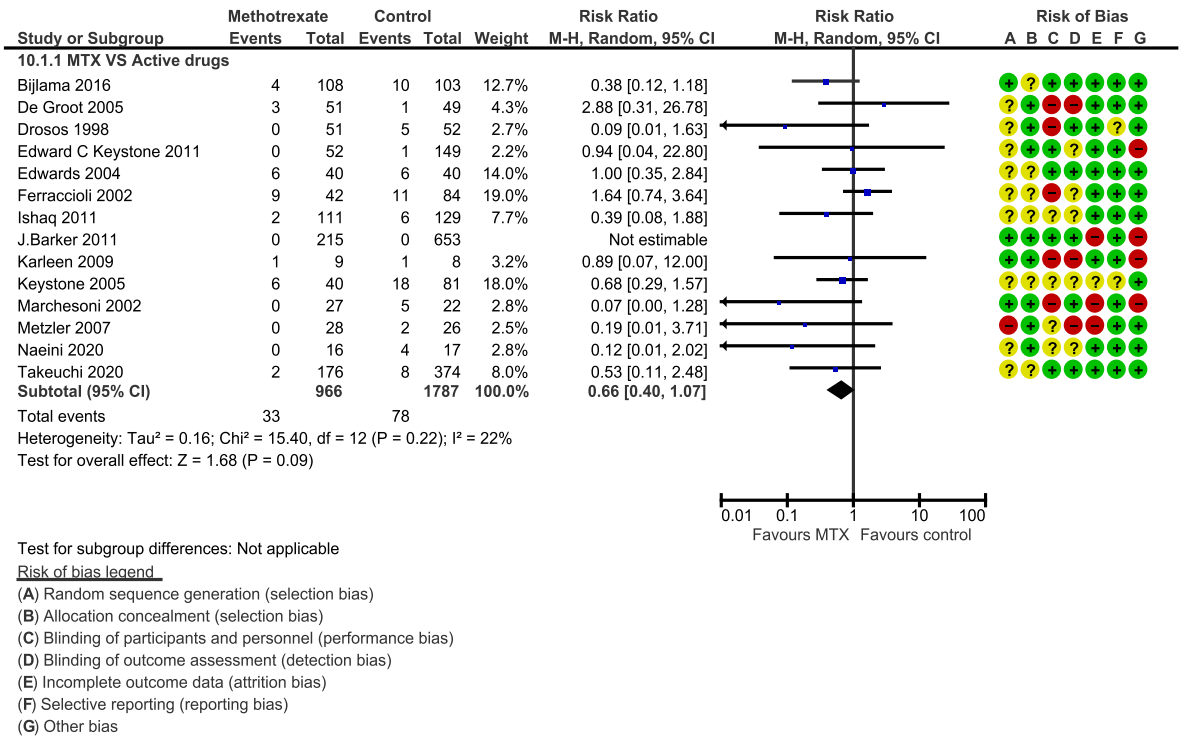

Figure 4-8 Sensitivity analysis for the association between the use of methotrexate and the risk of hypertension (RE model) after excluding studies that did not include the 95% CI.

4.3.2 Subgroup analyses

Table 4-2 summarise the subgroup analyses of MTX's impact on hypertension risk.

4.3.2.1 By type of comparator

The analysis, which included active drugs, was stratified by the type of comparator into four different subgroup analyses.

The RE model revealed a statistically significant lower risk of hypertension in methotrexate than cyclosporine (RR = 0.31, 0.08; 1.19, P = 0.09), indicating an average lower risk of 69% in methotrexate than cyclosporine. A total of 166 cases and 201 controls were included in the analysis, with fourteen and forty events, respectively, with substantial heterogeneity observed between studies (I^2 = 72%). The Ferraccioli study provided the highest weight (30.2%).

When the RE model was used to compare methotrexate to leflunomide, a statistically significant lower risk of hypertension was observed in methotrexate (RR = 0.32, 95% CI, 0.18; 0.55, P = 0.0001). No heterogeneity was observed between studies (I^2 = 0%). Two studies (Emery, Strand) contributed to ~85% of the meta-analysis weights.

Two studies compared methotrexate to anti-TNF ,619 and 1250 in methotrexate and the control groups, respectively. The estimate could not be calculated in one study due to the absence of events in both study arms. The RE model revealed a significantly lower risk of hypertension in methotrexate than in the control group (RR = 0.42, 95% CI, 0.23; 0.77, P = 0.005). No heterogeneity was observed between studies (I^2 = 0%). Finally, the risk of hypertension was not significantly different between methotrexate and rituximab (RR = 0.79, 95% CI, 0.41; 1.52, P = 0.48), with no heterogeneity observed between studies (I^2 = 0)(see **Figure 4-9).**

4.3.2.2 Clinical population setting

Only two studies included patients with HTN at baseline ,which had opposite effect sizes, although none of them were statistically significant. The pooled estimate from the RE model was not statistically significant (RR = 0.76, 95% CI, 0.49; 1.17, P = 0.21). The remaining twenty-four studies include patients with no HTN at baseline. The pooled estimate revealed a significantly lower risk of hypertension in patients who received methotrexate than those who received active comparators (RR = 0.50, 95% CI, 0.33; 0.73, P = 0.0005). Moderate to substantial heterogeneity was observed between studies (I^2 = 54%). The effect size was greater than one in only three studies and equal to one in two studies **(**see **Figure 4-10)**.

4.3.2.3 By duration of follow-up

The follow-up duration was < 2 years in seven studies and two years or more in the remaining nineteen studies. When the analysis was stratified by treatment duration, a significantly lower risk of hypertension was observed in patients who were followed up for < 2 years (RR = 0.46, 95% CI, 0.28; 0.75, P = 0.002). Patients who were followed up for 2+ years was not statistically significant (RR = 0.67, 95% CI, 0.45; 1.00, P = 0.05). (I^2 = 39%) and (I^2 = 40%) low heterogeneity was observed in both subgroups, respectively. For the former subgroup, 3146 and 3108 were included in methotrexate and the control groups, respectively, and the effect size was < 1 in six studies. For the latter subgroup, only three of the nineteen studies had an effect size > 1. **(**See **Figure 4.11).**

Table 4-2 The Summary of a meta-analytical subgroup analysis by RE model demonstrates the effect of methotrexate compared with control (placebo and active) on the risk of hypertension.

Subgroup analysis		Studies		Participant	event	Hypertension Incidence (%)		RR (M-H, Random, 95% Cl)	P value*	I^2 (%)
						MTX	Control			
Overall	RE	Placebo	5	5240	65	1.24	1.23	0.93 [0.61,1.44]	0.75	14
		Active drugs	21	6066	303	3.07	6.55	0.47 [0.34,0.65]	0.00001*	29
Type of comparator	Cyclosporine		5	367	54	8.43	19.90	0.31 [0.08,1.19]	0.09	72
	Leflunomide		4	1270	63	2.34	7.63	0.32 [0.18,0.55]	0.0001*	0
	Anti-TNF		3	1869	51	2.26	2.96	0.42 [0.23,0.77]	0.005*	0
	Rituximab		2	201	36	15	27.16	0.79 [0.41,1.52]	0.48	0
Clinical setting	Hypertension at baseline**		2	4828	32	0.58	0.74	0.76 [0.49,1.17]	0.21	0
	No hypertension at baseline**		23	6014	311	3.47	6.59	0.50 [0.33,0.73]	0.0005*	54
Duration of follow-up	Less than two years**		7	6254	125	1.20	2.79	0.46 [0.28,0.75]	0.002*	39
	Two years Or Longer**		18	4688	218	3.54	5.31	0.67 [0.45,1.00]	0.05	40

† **list of definitions and abbreviations**: Cl: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant.; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity.;** Placebo and active drugs have been combined.

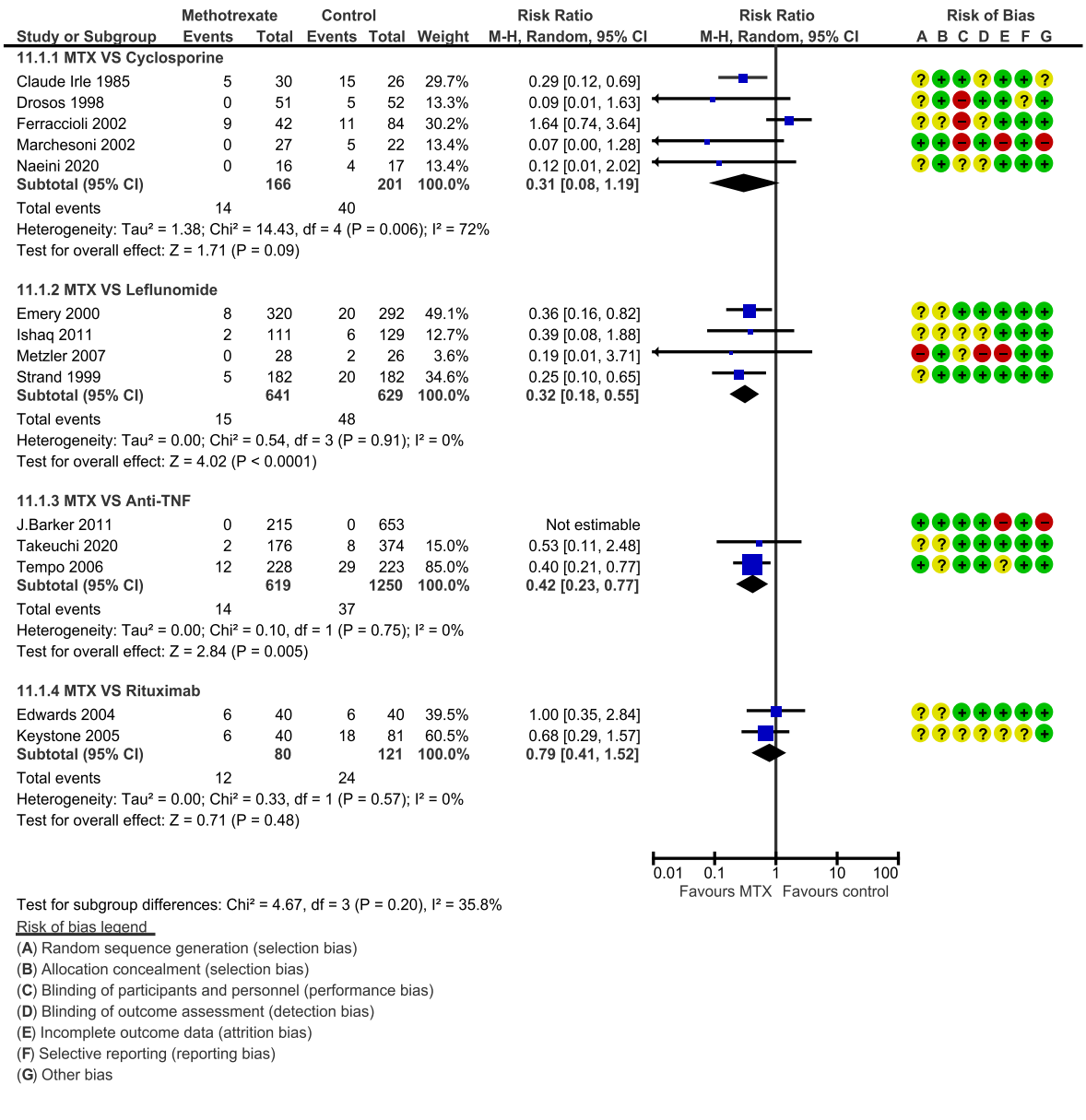

Figure 4-9 Subgroup analysis for the association between methotrexate and the risk of hypertension. (The analysis was stratified by comparator)

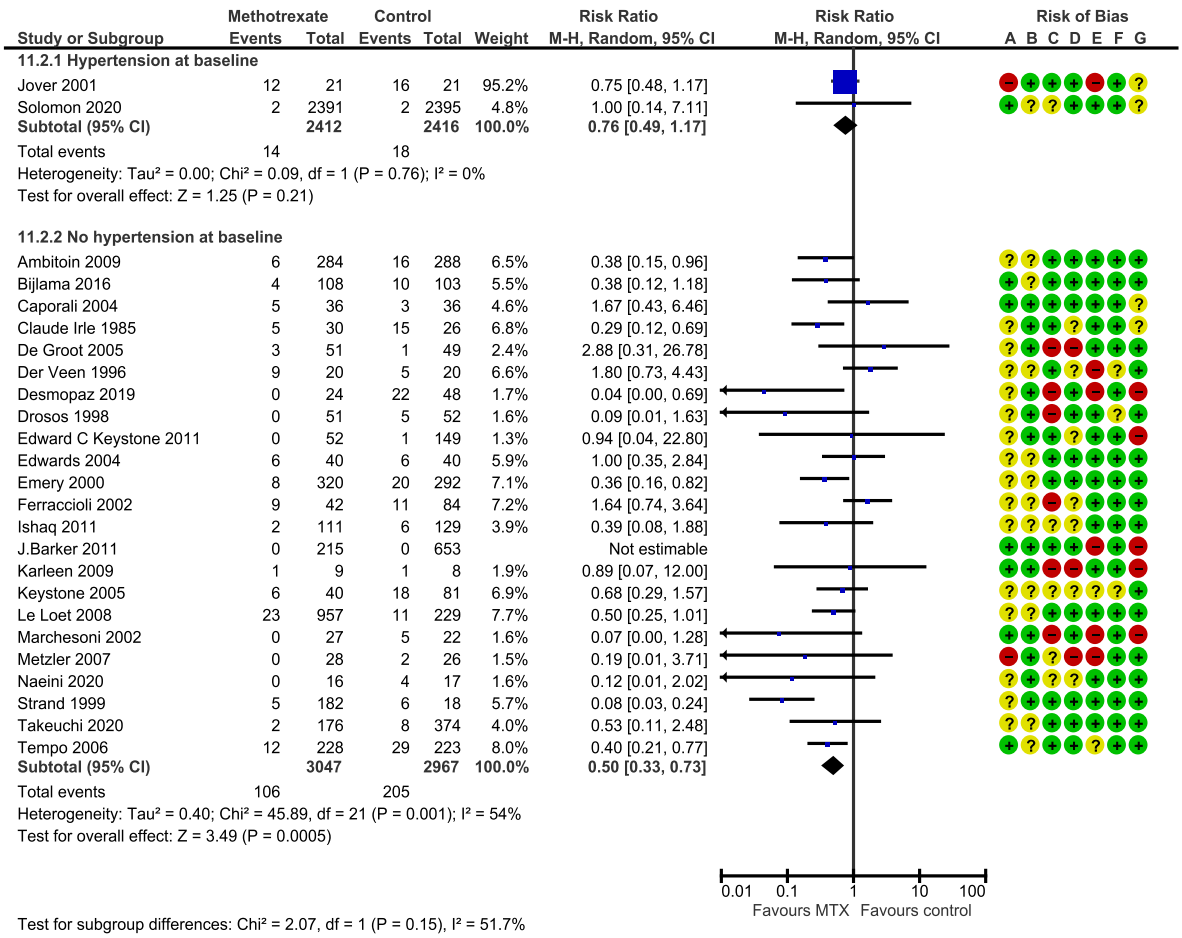

Figure 4-10 Subgroup analysis for the association between methotrexate and the risk of hypertension. (The analysis was stratified by clinical population setting)

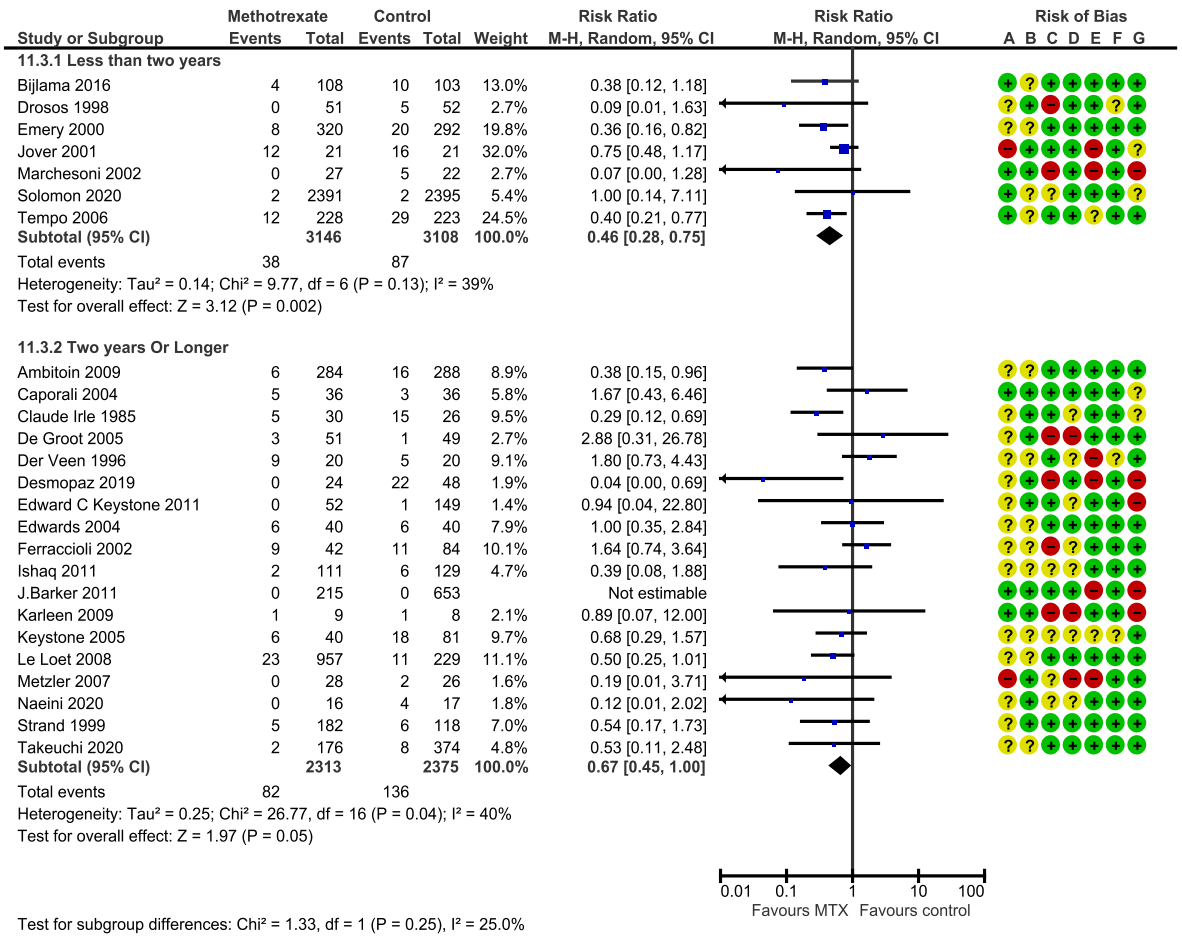

Figure 4-11 Subgroup analysis for the association between methotrexate and the risk of hypertension. (The analysis was stratified by the duration of follow-up. Placebo and active groups were combined)

4.4 Discussion

The most popular choice of disease-modifying antirheumatic therapy for rheumatoid arthritis and other conditions is methotrexate; results of studies have proven the impact of methotrexate on blood pressure and most studies showed hypertension as an adverse effect with a number of events.

The comprehensive systematic review and meta-analysis of methotrexate results indicate an influence on blood pressure with a 53% reduction in the risk of hypertension. When MTX was compared to other active drugs, a statistically significant difference was observed in the risk of hypertension between groups (RR = 0.47, 95% CI, 0.34; 0.65, P = 0.00001). When MTX was compared with the placebo, there was no significant difference in the risk of hypertension between them (RR = 0.93, 95% CI, 0.61; 1.44, P = 0.75). Once the fixed effects model was used in the analysis, the results did not change which means random effects and fixed effects models tally with the risk reduction of hypertension incidence in the methotrexate group compared to active drugs.

Several studies have confirmed the beneficial effects of immunosuppressant drugs, such as methotrexate, in terms of lowering blood pressure and reducing the incidence of cardiovascular events and mortality rates (Mangoni et al., 2017a, Yang et al., 2016). Mangoni et al. (2017b) attempted to discuss the plausibility of evidence regarding the effects of methotrexate on the cardiovascular system. In their review, hypertension is a key risk factor mediating cardiovascular dysfunction in rheumatoid arthritis (RA). Their review of the evidence indicates a blood-pressure-lowering mechanism due to the action of methotrexate. The studies included in the review indicated a lower systolic or diastolic blood pressure or both. Methotrexate has proved superior to disease-modifying-antirheumatic drugs (DMARDs) as a result of reduced CVEs mediated by atherosclerosis. In another cross-sectional study, researchers established that methotrexate in the treatment of RA contributed towards lower central blood pressure and possibly lower cardiovascular risk (Mangoni et al., 2017a).

In sensitivity analysis, after excluding the studies with a high risk of bias, the results showed no association between methotrexate and the incidence of hypertension in the placebo subgroup (RR = 0.89, 95% CI, 0.40; 2.00);the opposite

of that was significant in active drugs which showed no difference after studies were excluded. Studies with a small sample size of less than 100 participants were excluded in both subgroups. The placebo subgroup indicated that the risk of hypertension is not significantly different between methotrexate and the placebo arm (RR = 0.63, 95% CI, 0.23; 1.73) but still significant in the active drugs subgroup (RR = 0.41, 95% CI, 0.3; 0.56). Excluded studies did not include 95% Cl which showed that in active drug comparisons the estimate was not statistically significant (RR = 0.66, 95% CI, 0.40; 1.07, P = 0.09) which means that excluded studies have a huge influence on the rest of the group.

Active drugs were stratified by the type of the comparator into four different subgroup analyses. In the first comparator, cyclosporine, there were no significant differences in risk of hypertension between MTX and Cyclosporine (RR = 0.31, 0.08; 1.19, P = 0.09) ,the findings of the Claude Irie trial demonstrated that of the twenty six patients in the cyclosporine group, more than half experienced a hypertension incident. Comparing methotrexate to leflunomide, a statistically significant lower risk of hypertension was observed in methotrexate (RR = 0.32, 95% CI, 0.18; 0.55, P = 0.0001). Methotrexate was compared to anti-TNF; the result showed a significantly lower risk of hypertension in methotrexate (RR = 0.42, 95% CI, 0.23; 0.77, P = 0.005). Leflunomide was compared to placebo, methotrexate, and sulfasalazine in a meta-analysis study to evaluate its safety and effectiveness, which resulted in a higher risk of hypertension in patients that received leflunomide (Golicki et al., 2012). RCT trials were included in the meta-analysis showing that 6,321 Patients with RA who received anti-TNF therapy had a significantly greater chance of developing hypertension (Zhao et al., 2015). These previous study findings show evidence that many therapies displayed a high hypertension risk and demonstrates to the present study that methotrexate has the ability to control and lower blood pressure.

A study divided into a subgroup with HTN patients at baseline whose pooled estimate was not statistically significant (RR = 0.76, 95% CI, 0.49; 1.17, P = 0.21), and another subgroup with no HTN patients at baseline in which the pooled

estimate revealed a significantly lower risk of hypertension in patients who received methotrexate than those who received active comparators (RR = 0.50, 95% CI, 0.33; 0.73, P = 0.0005).

The follow-up duration was divided in two classes. A significantly lower risk of hypertension was observed in patients who were followed up for < 2 years (RR = 0.46, 95% CI, 0.28; 0.75, P = 0.002). The risk for patients who were followed up for 2+ years was not statistically significant (RR = 0.67, 95% CI, 0.45; 1.00, P = 0.05).

According to a case-control study, taking methotrexate effectively suppresses inflammation, which prevents the formation of atherosclerosis and, ultimately, clinically apparent cardiovascular disease, which proved that taking MTX lowers the risk of developing CVD significantly (van Halm et al., 2006). In a meta-analysis of observational studies, the results showed that usage of methotrexate was associated with reduced risk of CVD in those who suffer from ongoing inflammation (Micha et al., 2011).

Thirty psoriasis patients were enrolled in a prospective randomised comparison trial, and they were randomly assigned to receive methotrexate alone (MTX) or methotrexate with intramuscular vitamin D (MtxD) for three months. The MTX group's systolic and diastolic blood pressure were observed to decrease significantly but only diastolic blood pressure dropped in the MtxD group (El-Hanafy et al., 2022).In 2017, Woodman showed that whereas elevated arterial stiffness preceded rises in blood pressure in RA participants, similar effects did not occur in MTX-using patients. The positive benefits were primarily noticeable in SBP, but they were also observable to some level in DBP, especially when it came to the more precise evaluation of 24-hour blood pressures. These results imply that MTX may provide a protective effect against stiffness-mediated elevations in blood pressure in RA patients. (Woodman et al., 2017b). Users of methotrexate and hydroxychloroquine had the most considerable reduction; after six months of treatment, people using methotrexate were 9% more likely to have ideal blood pressure (BP). In comparison, patients treated with leflunomide experienced higher blood pressure and a higher risk of developing incident hypertension (Baker

et al., 2018).To summarise, the results of several previous studies join a growing body of evidence supporting the hypothesis that treatment with methotrexate has beneficial effects on blood pressure.

4.5 Strength and limitations

This review is the largest meta-analysis of RCTs investigating MTX and the risk of hypertension and incorporates all publicly available data reported to date. Furthermore, unpublished hypertension data from the Solomon, J. Barker, and Takeuchi trials were included in this meta-analysis, which will improve the quality of the evidence. The reliability of the results across several sensitivity analyses assist the robustness of the primary results. Additionally, the pooling of results from all of the included trials was supported by the low statistical heterogeneity.

Nevertheless, there are important limitations in our analysis. Hypertension, which is usually reported as an adverse event, was not designed to be detected as a primary outcome in any of the included trials. The majority of studies have small sample sizes, except Solomon, which was slightly larger, but an extensive sample size is required to allow a more precise estimate of the treatment effect. All RCTs have a short average follow-up period of four months to five years. Therefore, this meta-analysis reports the risk of bias because some studies have unclear allocation sequences described without further details, insufficient detailing of concealment schemes or stratification, and incomplete information.

There was a possibility that unpublished studies might have been missed despite a thorough, comprehensive search of databases and clinical trial registers.

4.6 Conclusion

This meta-analysis of RCTs used data from 11,265 patients. The years of follow-up has shown that MTX reduces the risk of hypertension compared to active drugs in patients with various autoimmune disorders. The results of direct comparison trials further support the idea that MTX is more protective against the risk of hypertension.

5. Association between Anti-TNF inhibitors and risk of hypertension

5.1 Introduction

A new generation of rheumatology drugs, which including monoclonal antibodies, a cytokine mimic and two fusion proteins, has been developed to fill the gaps left by treatments such as methotrexate (Jawa et al., 2020). TNF-Inhibitors include the monoclonal antibody-based proteins infliximab, adalimumab, certolizumab, the fusion protein etanercept and golimumab. In 1989, discovered that TNF inhibition can reduce the production of various proinflammatory cytokines, based on advances in antibody engineering (Brennan et al., 1989). TNF-Inhibitors showed some positive effects on animal models used for arthritis and it has been shown that TNF-Inhibitors can be used to treat people with rheumatoid arthritis (Kumar et al., 2005). The Food and drug administration and European medicines agency have approved five TNF-Inhibitors, namely infliximab, certolizumab pegol, etanercept, adalimumab and golimumab. A chimeric IgG1 antibody, etanercept, derived from human IgG1, certolizumab pegol and TNF-receptor type 2, a humanised anti-TNF antibody with a fragment of PEGylated Fab, are all marketed by a number of pharmaceutical firms (Tragiannidis et al., 2017).Both golimumab and adalimumab are completely human IgG1 antibodies. These medications can be very helpful in the treatment of inflammatory disorders such as rheumatoid arthritis, but there remain barriers to their widespread application, namely their scarcity and the adverse reactions they cause, particularly the drug adalimumab (Shealy et al., 2010).

Infliximab is a human tumor necrosis factor chimeric monoclonal antibody that is used in this therapy. Infliximab can significantly reduce levels of systolic blood pressure, especially in the morning. This reduction can be correlated with reduced inflammation patterns (Yoshida et al., 2014). As the first anti-TNF biologic to be released, infliximab (a chimeric monoclonal antibody) has been used clinically to treat rheumatoid arthritis and other inflammatory diseases since the late 1990s. Infliximab was approved by FDA in October 1998 for the treatment of moderately to highly active Crohn's disease, as well as for

fistulising it (Lee et al., 2002). There are some adverse effects associated with infliximab, some of which can be life-threatening, as with other TNF-inhibiting immuno-suppressive medications. (Chen et al., 2017).

TNF-inhibiting biologic medications, such as certolizumab, adalimumab, golimumab and etanercept, are now available (Willrich et al., 2015). Etanercept competes with proinflammatory cytokine TNF-α, which is suggested for both the etiology and treatment of psoriasis and psoriatic arthritis (Goffe and Cather, 2003).Etanercept is helpful in the treatment of patients with rheumatoid arthritis and psoriatic arthritis, reducing psoriatic skin lesions. Based on these findings, an evaluation was made of two distinct etanercept regimens in individuals with a moderate-to-severe psoriasis condition (Sterry et al., 2010).

Certolizumab is the only PEGylated anti-TNF biologic currently licensed for Crohn's disease and rheumatoid arthritis. A polyethylene glycol-bound humanised form of the antigen-binding fragment of monoclonal antibody is used to make the product from UCB. Certolizumab pegol was approved as a therapy for rheumatoid arthritis in 2009 in the European Union (EU), the United States (US) and Canada. It was approved in the US in 2007 and 2008 to be used for Crohn’s disease. Clinical data show that certolizumab pegol improves clinical, radiological and patient-reported outcomes, but it is entering a market that is becoming increasingly competitive, especially in the field of rheumatoid arthritis (Goel et al., 2010) . According to the FDA, the drug was approved in May 2009 for the treatment of moderate-to-severe rheumatoid arthritis in adults, as a monotherapy or in combination with disease-modifying anti-rheumatic medications (Rivkin, 2009). There have been reports of a number of adverse reactions among Crohn’s patients, such as serious infections including sinusitis, otitis media, nasopharyngitis, urinary tract infection, folliculitis, cervical, oral and vaginal herpes, clostridium difficile, gluteal and labial infections, and herpes zoster infections (Moon et al., 2015).

In April 2009, golimumab, a monoclonal antibody against TNF, was approved for the treatment of ankylosing spondylitis, psoriatic arthritis and rheumatoid

arthritis (Pappas et al., 2009).In combination with methotrexate, the medication may be prescribed to adults with moderate-to-severe conditions of rheumatoid arthritis, psoriatic arthritis and active ankylosing spondylitis, either acting alone or in combination with methotrexate (Gasparyan et al., 2012). In addition to its use for ulcerative colitis and severe persistent asthma, golimumab has been investigated as a treatment for both conditions throughout its clinical development (Mazumdar and Greenwald, 2009).

Adalimumab, a monoclonal IgG1 recombinant antibody, inhibits the inflammatory effects of TNF in patients with active rheumatoid arthritis who are receiving DMARDs therapy. Well-designed studies have used subcutaneous adalimumab in patients with active rheumatoid arthritis (Chames et al., 2009).The FDA approved the adalimumab injection, on February 24 2021, as an efficacy supplement that can treat a moderate-to-severe active condition of ulcerative colitis in children aged 5 and older (Li et al., 2022).

5.1.1 Mechanism of Action of TNF-Inhibitors

Monocytes and macrophages activate the release of TNF in response to inflammatory stimuli. TNF is a Type-II trans-membrane protein (Kaymakcalan et al., 2009). A TNF superfamily member is cleaved into 17 kDa TNF proteins, which are then physiologically active as 51 kDa trimetric forms. Both TNFs have a variety of functions that interact with 54 receptors, of which 53 are physiologically active (Chen, 2012).The Fc region of modified monoclonal antibodies is generally human, in order to ensure it has favorable pharmacokinetic characteristics (Scallon et al., 1995). The Fab region may, however, be murine, mainly in the case of chimeric antibodies. All approved anti-TNF drugs, except etanercept, are monovalent Fab antibody fragments or full-length monoclonal antibodies, like infliximab, adalimumab or golimumab. Etanercept is a fusion protein that has been genetically modified; it is composed of an Fc fragment. To increase its solubility and half-life, polyethylene glycol is covalently linked to the hinge region of certolizumab. Since it is a Fab fragment with no Fc region, it does not possess effects or functions. The monoclonal antibodies adalimumab and golimumab are 100%

humanized monoclonal antibodies (Prado et al., 2017). Additionally, certain agents can be recognized by their various kinetic properties. Adalimumab and infliximab have a slower rate of on- and off- than etanercept. Furthermore, while infliximab can bind both 51 kDa trimers and 17 kDa monomers of TNF, etanercept can only bind the 51 kDa trimer form of TNF. Both infliximab and adalimumab can bind two sol-TNF trimers at once. It has been found that all five anti-TNF medications bind to sol-TNF with its high affinity, with etanercept having intrinsic binding affinities that are greater than those of either infliximab or adalimumab. Etanercept has a higher avidity than adalimumab and infliximab, according to research. In the same study, it was shown that the binding affinities/avidities of infliximab, etanercept and adalimumab for tm-TNF were comparable (Posner et al., 2019).

The mechanism of action of medications in TNF-Inhibitors is mainly based on the inhibition of proinflammatory cytokines. TNF exists in two forms, namely tmTNF and sTNF. Binding of TNF to the receptors initiates proinflammatory signaling in cellular apoptosis and the activation of these cytokines. The common mechanisms of these monoclonal antibodies in the neutralization of TNF, as depicted in **Figure 5-1**, include reverse signaling, antibody-dependent cell cytotoxicity and the induction of regulatory macrophages.

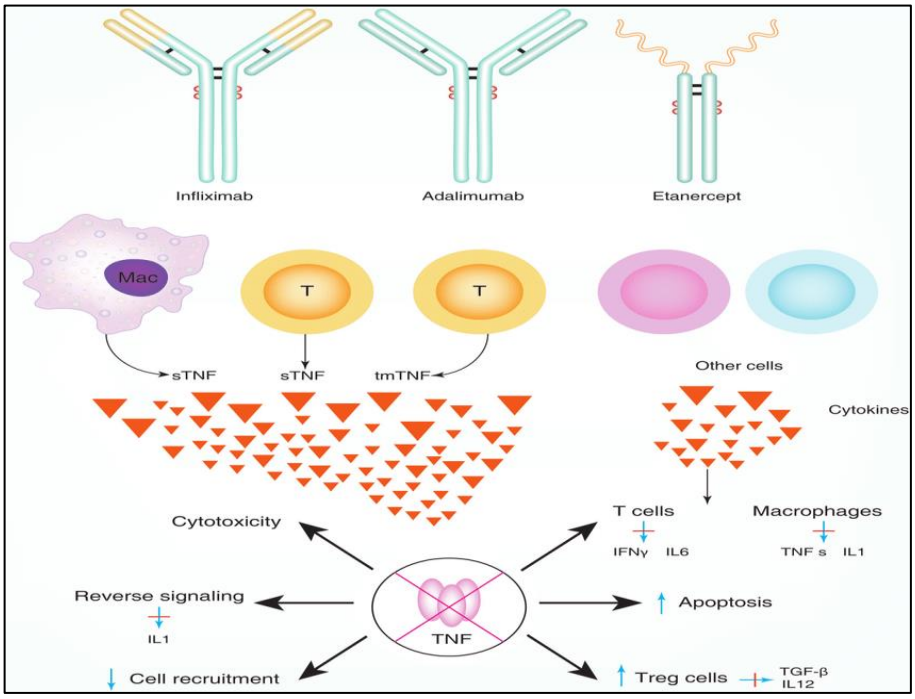

Figure 5-1 TNF-Inhibition by reverse signalling, antibody-dependent cell cytotoxicity and the induction of regulatory macrophages.

Adapted from (Kapuria and Chhabra, 2017)

5.1.2 Hypothesis from Basic Science

Some previous investigations into the effect of TNF-Inhibitors on blood pressure and hypertension damage in experimental models of hypertension (pre-clinical studies) can provide a justification for the current research. So to understand the effects these medications on the hypertension some previous experimental funding suggest different results. These are mentioned in **Table 5-1**.

Table 5-1 The findings from selected preclinical studies

Study (Year)	Design of the Study	Animals Used	Results and Summary	References
Infliximab prevents increased systolic blood pressure and up-regulates the AKT/eNOS pathway in the aorta of spontaneously hypertensive rats.	Lab Test	Rats	The study demonstrated that the TNF-Inhibition caused by infliximab reduced blood pressure in rats. The reduction was associated with the up-regulation of AKT/eNOS.	(Gazzoto Filho et al., 2013)
Constitutive smooth muscle tumour necrosis factor regulates microvascular myogenic responsiveness and systemic blood pressure.	Lab Test	Mice	The study demonstrated that anti-TNF therapy induces a significant drop in systolic, as well as diastolic, blood pressure. The use of anti-TNF medication lowered the risk of hypertension independently of inflammation by any non-endothelial mechanism.	(Kroetsch et al., 2017)
Effect of infliximab and tocilizumab on fructose-induced hyperinsulinemia and hypertension in rats.	Lab Test	Male Wistar rats	The main finding of this study was that infliximab and tocilizumab were able to partially reverse increased blood pressure in male Wistar rats. The study also claimed that this was a novel finding.	(Abdelrahman et al., 2018)

5.1.3 Rationale for the current Study

Several studies involving human subjects have been carried out to understand the effects of TNF-Inhibitors on hypertension, and to investigate how these regulate blood pressure when used to treat any kind of inflammatory disorder. An example of such a clinical study is the one carried out by Zhao et al. (2015) to investigate the dose-dependent adverse reactions of TNF-Inhibitors, including hypertension, this study suggested that these medications are associated with the development of hypertension. A double-blind, placebo-controlled trial by Faria et al. (2021) , whose main research question was whether a single dose of infliximab could reduce blood pressure in patients with rheumatoid arthritis, indicated that there was an acute decrease in diastolic blood pressure after the administration of the infliximab. The **table 5-2** below lists various clinical studies that have been conducted to investigate the effects of some drugs on the risk of hypertension.

Table 5-2 Findings of selected previous clinical studies

Study	Design of the study	Patients	Follow up period	Intervention	Comparators	Summary
Tumour TNF inhibitors use and the risk of incident hypertension in patients with rheumatoid arthritis (Desai et al., 2016)	Cohort study	6,862 patients, Rheumatoid arthritis	14 weeks	TNF-α inhibitors	Non-biologics	The final results suggested that the risk related to CVS may mediate beneficial effects other than high blood pressure
Reduction in incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-TNF therapy (Dixon et al., 2007)	Prospective observational study	2,170 patients Rheumatoid arthritis	24 weeks	TNF-Inhibitors	DMARDs	The use of these medications did not cause any changes in the levels of blood pressure.
Infliximab, a TNF-Inhibitors reduces 24-h ambulatory blood pressure in rheumatoid arthritis patients (Yoshida et al., 2014)	Clinical trials	16 patients	32 weeks	Infliximab		Infliximab can reduce ambulatory blood pressure in patients with rheumatoid arthritis

5.2 Methodology

5.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

5.2.2 Data extraction

The initial search yielded 737 articles using the search strategies detailed in the **Appendix A**, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of the research (see **Figure 5-2**).

After removing duplication, the remaining 451 citations or abstracts were assessed for inclusion criteria. At that point, 349 articles were eliminated based on a title and abstract review process, almost 87% of the total, as predefined by the PICOS criterion. Of the 102 publications that remained for eligibility studies, sixty-three RCTs were eliminated after a full-text screening for several reasons which are described in **chapter 3,Table 3-1**.Ultimately, forty trials with 16,423 patients enrolled for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

5.2.3 Description of excluded studies

A total of sixty-two publications were excluded after an extensive eligibility check of their full text. Twenty-seven trials (Bingham, Davis ,Dirckx, Duggan, Elewski, Emery, Faria, Jinhua, Furst, Giles, Holzer, Sycamore Kirkham, Kavanaugh, Keystone, Kimball, Lan, Mansur, Menter, Park ,Puig, Rau, Schreiber, Tempo trial ,Atlas trial, Wascher and Westhovens) reported different outcomes, which did not mention hypertension (HTN).

Two studies (Tremoulel and Wang) had a follow-up period under three months; hypertension is known to show clearly after three months. Two studies (Seo and Smolen) were removed for having a different display, which was the Cohort design.

The most excluded type of studies were those who had used Anti-TNF in both arms, abstracts, annual meetings, and conferences.**Chapter 3,Table 3-1** summarises the reasons for the elimination of each trial.

5.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.

Sensitivity analyses were completed by the exclusion of trials with [1] poor methodological qualities; [2] small sample sizes with less than 100 total participants; and [3] excessively large sample sizes.

Subgroup analyses for Anti-TNF were performed as follows: (1) comparator drugs; (2) clinical setting; (3) duration of follow-up.

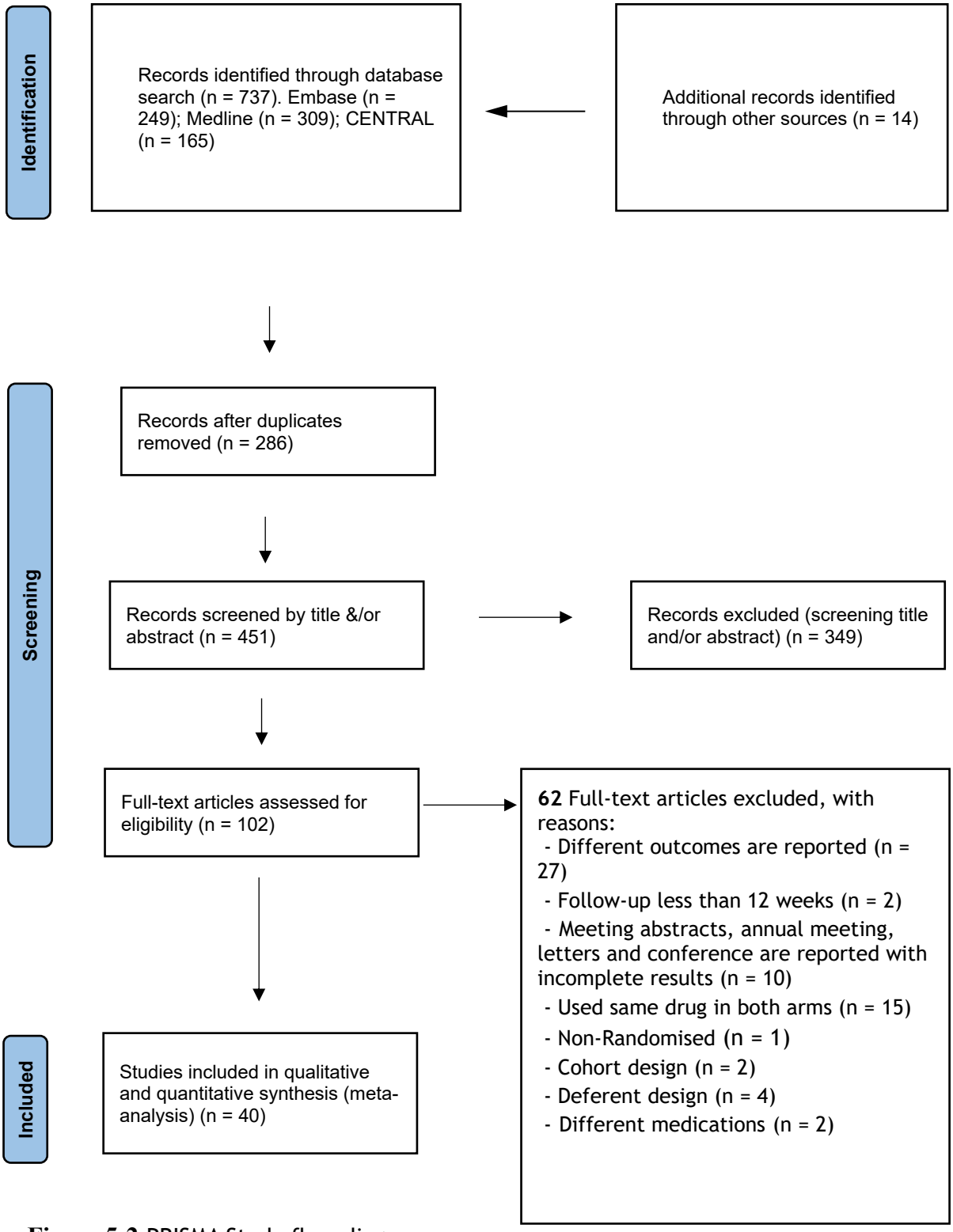

Figure 5-2 PRISMA Study flow diagram

5.3 Results

In total, forty eligible Anti-TNF trials with 16,423 patients were enrolled, with an average follow-up period of 1 year (range three months to four years).
The average patient age for all trials was forty-nine years old.
The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

Figure 5-2 provides a summary of the trial searching and identification process. sixty-two studies were excluded for logical reasons.
Table 3-1 in chapter 3, records the reasons for the excluded studies and forty RCTs (randomised controlled trials) were used for the final review.

The majority of studies have been published since 2003. However, there is one study (Maini), published in 1999. It compared Infliximab with placebo; four hundred and twenty-eight patients with rheumatoid arthritis received methotrexate, and hypertension and other conditions were reported as incidences.

Some studies were published from two thousand three to two thousand ten, such as those by Brzezicki, Emery, Gottlieb, Grant, Kavanaugh, Kerhof, Mease, Menter, Salvarani, Smolen, Westhovens, Combe, and Tempo.

The Gottlieb study, published in 2003, investigated the effect of etanercept in the treatment of psoriasis, and reported a number of patients experiencing adverse effects, one of which was hypertension.

Thirty studies compared different types of TNF inhibitors with a placebo, and all of them reported hypertension as an adverse event.
Ten studies compared Anti-TNF to active controls involving Sulfasalazine, anti-17, anti-6, MTX, Ustekinumab. Some of these were divided into subgroups (See **Figure 5-8**) and others were not because each drug had only one study which cannot be used for the purposes of meta-analysis.

Most of the studies employed a double-blind design except for two (Giles and Restore 1) who used an open-label design. One study (Westhovens) did not specify the nature of the design, whether it be open or double-blind. None of the studies implemented a factorial design.

The follow-up study periods were at least three months and the most extended was four years. All the study participants were adults with a mean age of over forty years old. All participants in the studies were male and female but differ in proportion from study to study.

In most studies, the patients have been diagnosed with rheumatoid arthritis, some of them have also been diagnosed with other diseases such, axial spondylarthritis, psoriasis, and dermatomyositis. All the relevant details are described in **Table 5-3**.

Table 5-3 The underlying disease of each trial.

Trial	Background disease	Trial	Background disease
Aitken	erosive hand osteoarthritis	Salvarani	polymyalgia rheumatica
Amato	dermatomyositis	Schiff	Rheumatoid arthritis
Brzezicki	Rheumatoid arthritis	Sieper	axial spondyloarthritis
Butchart	alzheimer's disease	Smolen	Rheumatoid arthritis
Deodhar	axial spondyloarthritis	Vollenhoven	Rheumatoid arthritis
Emery	Rheumatoid arthritis	Westhovens	Rheumatoid arthritis
Ferraccioli	Rheumatoid arthritis	Yamamoto	Rheumatoid arthritis
Go-Further	Rheumatoid arthritis	Adacta	Rheumatoid arthritis
Gottlieb	psoriasis	Combe	Rheumatoid arthritis
Grant	hidradenitis suppurativa	Glies	Rheumatoid arthritis
Hikari	Rheumatoid arthritis	Restore 1	Plaque psoriasis
Holgate	Sever-Asthma	Mclnnes	psoriatic arthritis
Judson	sarcoidosis	Monarch	Rheumatoid arthritis
Kavanaugh	psoriasis	Sirround-H	Rheumatoid arthritis
Kerhof	Plaque psoriasis	Takeuchi	Rheumatoid arthritis
Keystone	Rheumatoid arthritis	Tempo	Rheumatoid arthritis
Landewe	ankylosing spondylitis	Mease	psoriatic arthritis
L Cai	Plaque psoriasis	Menter	Plaque psoriasis
Maini	Rheumatoid arthritis	Hall	pemphigus vulgaris
Regueiro	Crohn’s disease		

Anti-TNF was compared to a placebo in thirty studies which included 9,111 patients. 6195 in the Anti-TNF group and 2916 in the placebo group. A total of 229 (3.7%) and 81 (1.3%) events occurred in Anti-TNF and the placebo groups, respectively. The random-effects meta-analysis showed that the risk of hypertension was significantly higher in Anti-TNF than the placebo group (RR = 1.31, 95% CI 1; 1.73, P = 0.05). Westhovens study contributed to 16 % of the meta-analysis weight. Low heterogeneity was observed between studies (I2 = 2%, P = 0.43). The effect size was not statistically significant within any of the individual studies and could not be estimated within one study due to the absence of events in both groups.

Anti-TNF was compared to other active drugs in ten studies which included 7312 patients. A total of 90 and 85 events occurred in Anti-TNF and the active drug groups, respectively. The risk of hypertension was not significantly different between Anti-TNF and other active drugs (RR = 1.14, 95% CI 0.73; 1.78, P = 0.56). Four studies (Adacta, Mclnnes, Sirround-H, and Temp) provided two-thirds of the weight for the meta-analysis. The risk of hypertension was the same as for other active drugs in all individual studies except for Tempo, which favoured the active drugs. Minimal heterogeneity was observed between studies (I2 = 38%, P = 0.11) **(**See **Figure 5.3).**

The fixed-effects model supported the results obtained using the random effects model and showed that the risk of hypertension was significantly higher in Anti-TNF than the placebo (RR = 1.34; 95% CI 1.04; 1.73, P = 0.02). The risk of hypertension was not significantly different between Anti-TNF and other active drugs supporting the results obtained when the random-effects model was used (RR = 1.13, 95% CI 0.85; 1.52, P = 0.40). Mclnnes study provided one-quarter of the weight for the meta-analysis while studies Adacta, Sirround-H, and Temp contributed to 60% of the meta-analysis weight **(**See **Figure 5.4).**

Visual inspection of the funnel plot (**Appendix D, Figure D-2**) shows a missing study in the middle left of the plot, which appears as asymmetry. No outlier was detected.

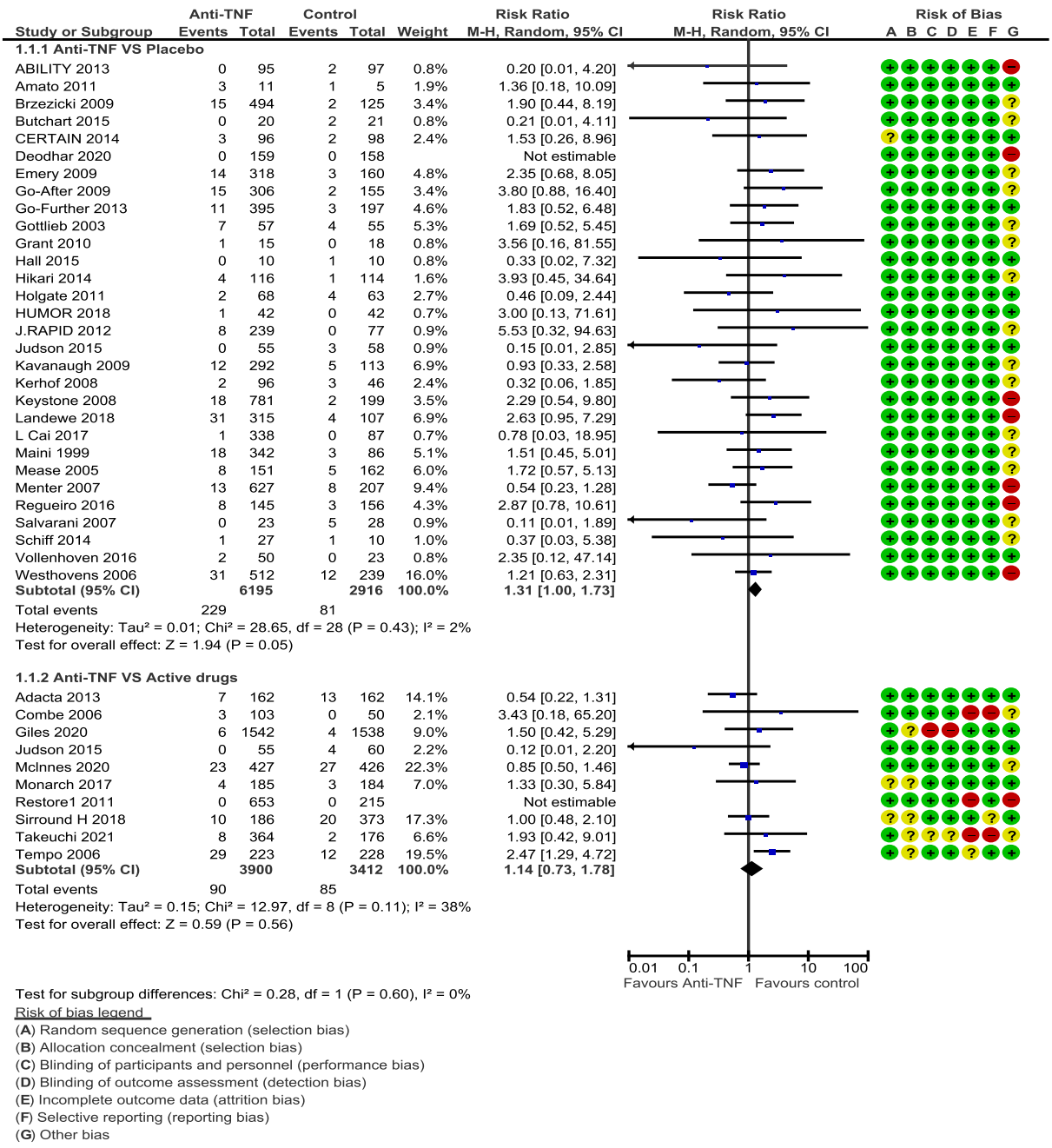

Figure 5-3 Random effects model for the association between Anti-TNF drugs and risk of hypertension.

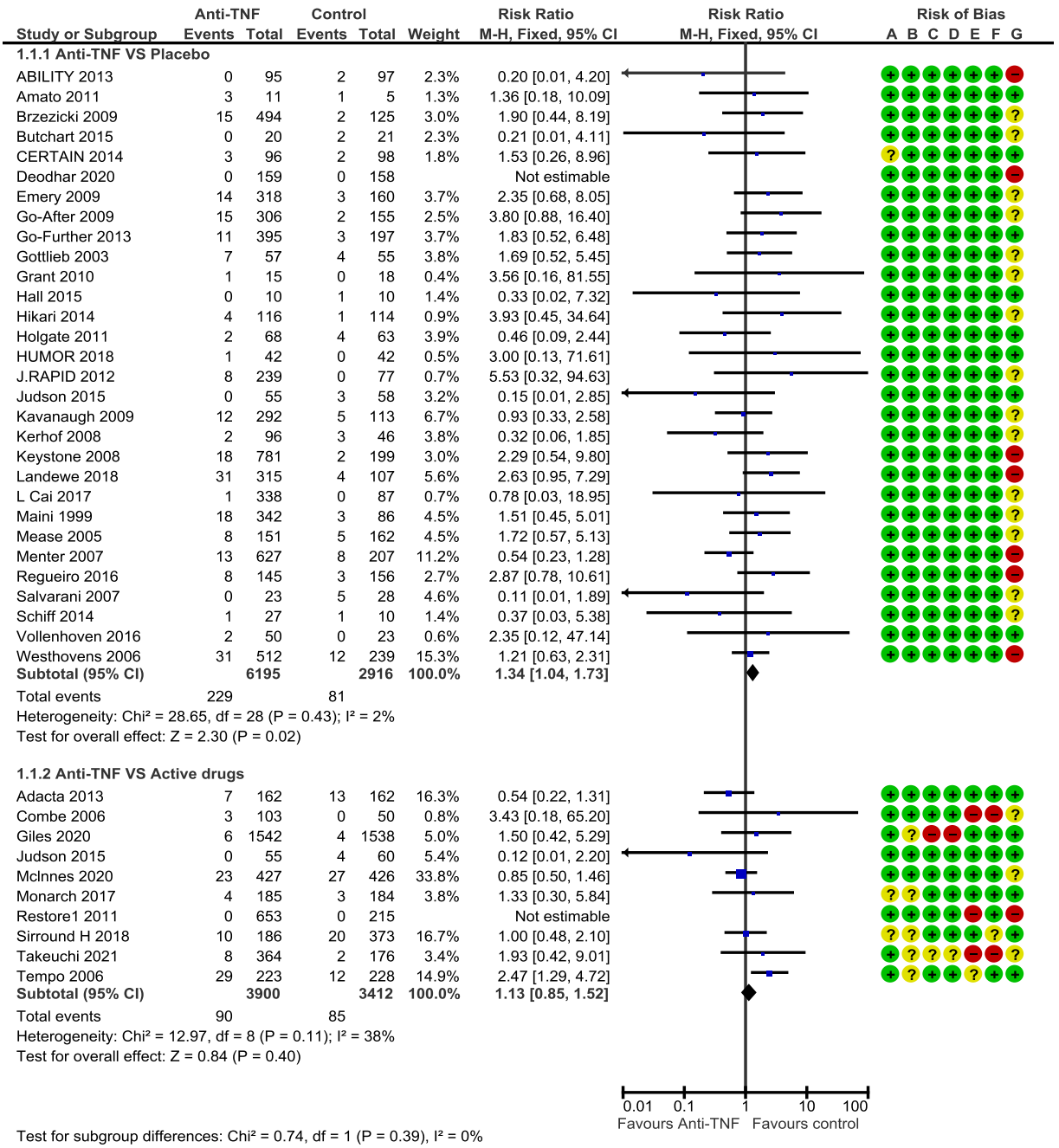

Figure 5-4 Fixed-effects model for the association between Anti-TNF drugs and the risk of hypertension.

5.3.1 Sensitivity analyses

Seven studies were excluded in the placebo arm, and one study were excluded in the active arm comparison. After excluding studies with high RoB, no association was observed between Anti-TNF and the risk of hypertension (RR = 1.34, 95% CI 0.94; 1.91, P = 0.1), indicating that the initial analysis results are not robust. The estimate was less than one in eight studies and greater than one in the remaining fifteen. The analysis included 3561 and 1753 patients in Anti-TNF and the placebo arms, respectively. No heterogeneity was observed between studies (I^2 = 0%).

Results did not change when high RoB studies comparing Anti-TNF to other active comparators were excluded. Results did not change, and the risk of hypertension was not significantly different between Anti-TNF and other active comparators (RR = 1.14; 95% CI 0.73; 1.78, P = 0.56). Low heterogeneity was observed between studies (I^2 = 38%) (See **Figure 5-5**).

As **figure 5-6** after excluding studies with small sample sizes, the anti-TNF was compared to a placebo in **sixteen** studies, including 7872 patients (5530 in the anti-TNF group and 2342 in the placebo group). The effect size could not be estimated in one study. A total of 207 and 53 events occurred in Anti-TNF and the placebo groups, respectively. The estimate from the RE model showed that the risk of hypertension was significantly higher in Anti-TNF than in the placebo group (RR = 1.52, 95% CI 1.12; 2.06, P = 0.007), supporting the original analysis, which included all studies. No heterogeneity was observed between studies (I^2 = 0%, P = 0.49). The effect size was not statistically significant within any individual study and could not be estimated within one study due to the absence of events in both groups. Anti-TNF was compared to other active drugs in nine studies, including 3845 and 3352 patients in Anti-TNF and placebo groups. A total of 90 and 81 events occurred in Anti-TNF and the active drug groups, respectively. Results did not change compared to the original analysis, and the risk of hypertension was not significantly different between Anti-TNF and other active drugs (RR = 1.19, 95% CI 0.79; 1.82, P = 0.41). Minimal heterogeneity was observed between studies (I^2 = 34%, P = 0.15).

Sixteen studies that compared Anti-TNF to the placebo group were excluded as they included more than 100 patients. The analysis included 665 and 574 patients in Anti-TNF and the placebo groups, respectively. No association was observed between the use of Anti-TNF and the risk of hypertension (RR = 0.76, 95% CI 0.43; 1.36, P = 0.36), although the estimate was lower in Anti-TNF. No heterogeneity was observed between studies (I^2 = 0%, P = 0.59). None of the included studies showed a statistically significant association between the use of Anti-TNF and hypertension (See **Figure 5-7**).

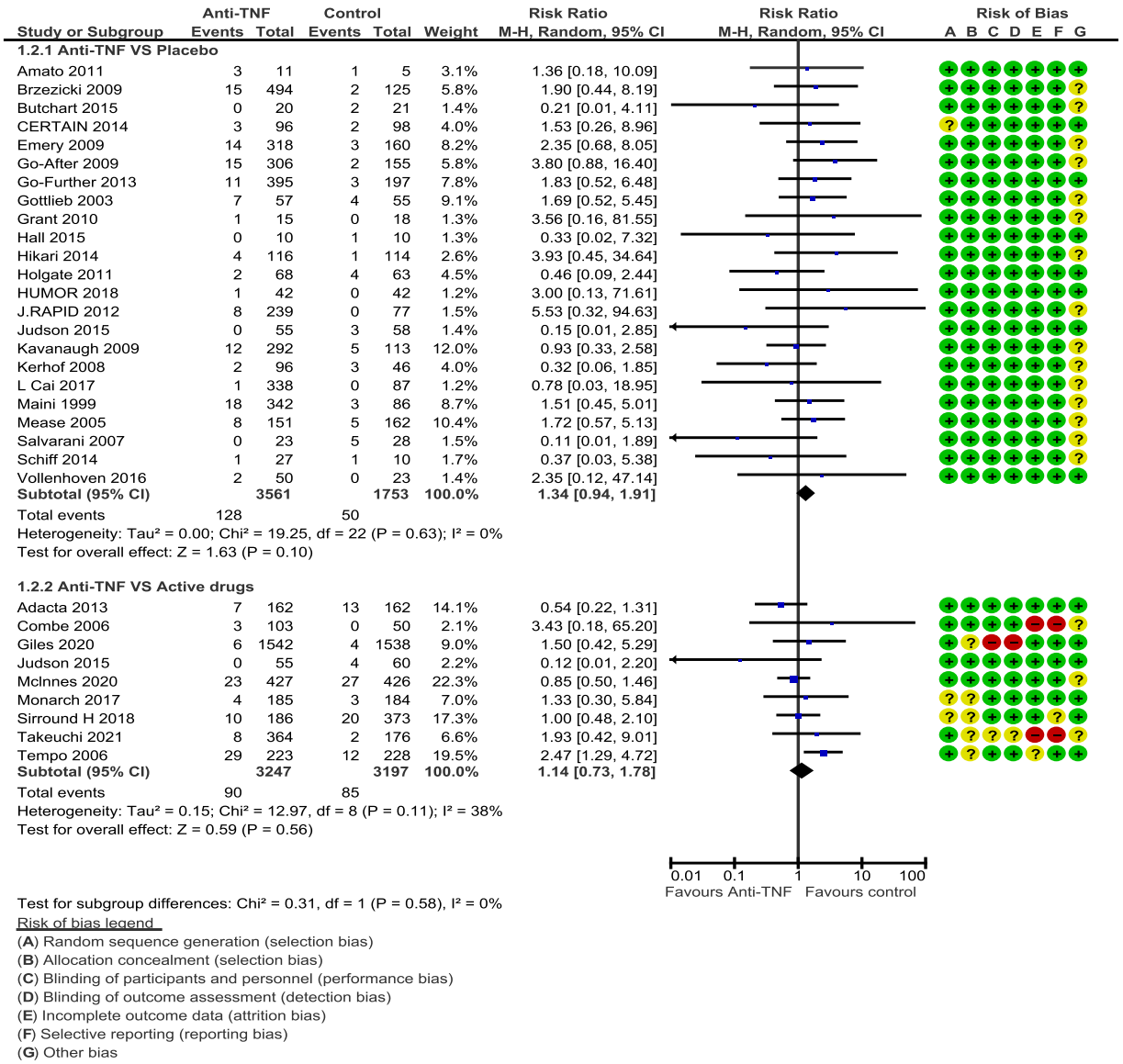

Figure 5-5 RE model for the association between the use of Anti-TNF drugs and the risk of hypertension. Studies with a high risk of bias were excluded.

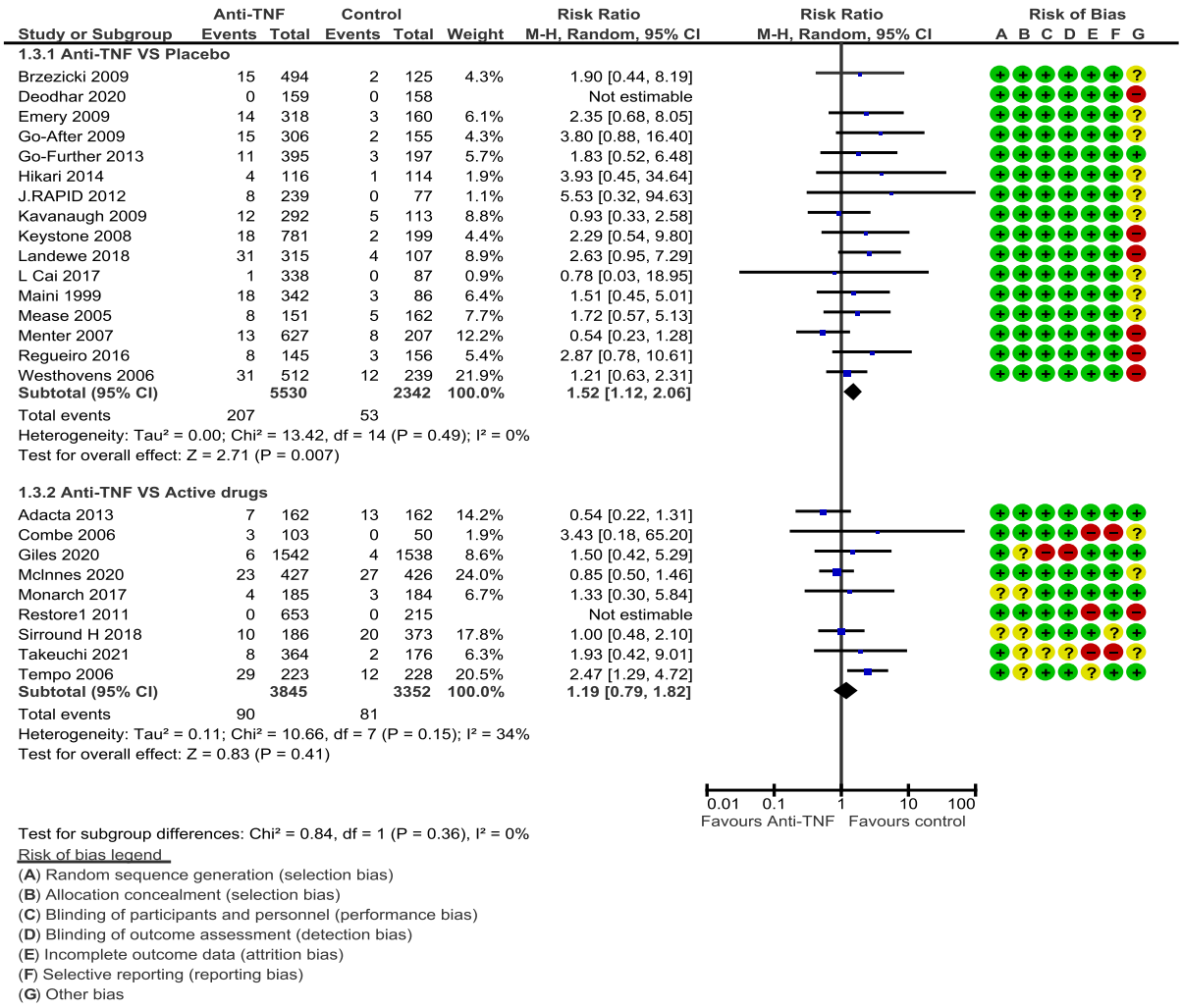

Figure 5-6 RE model for the association between the use of Anti-TNF drugs and the incidence of hypertension. Studies with less than 100 patients were excluded.

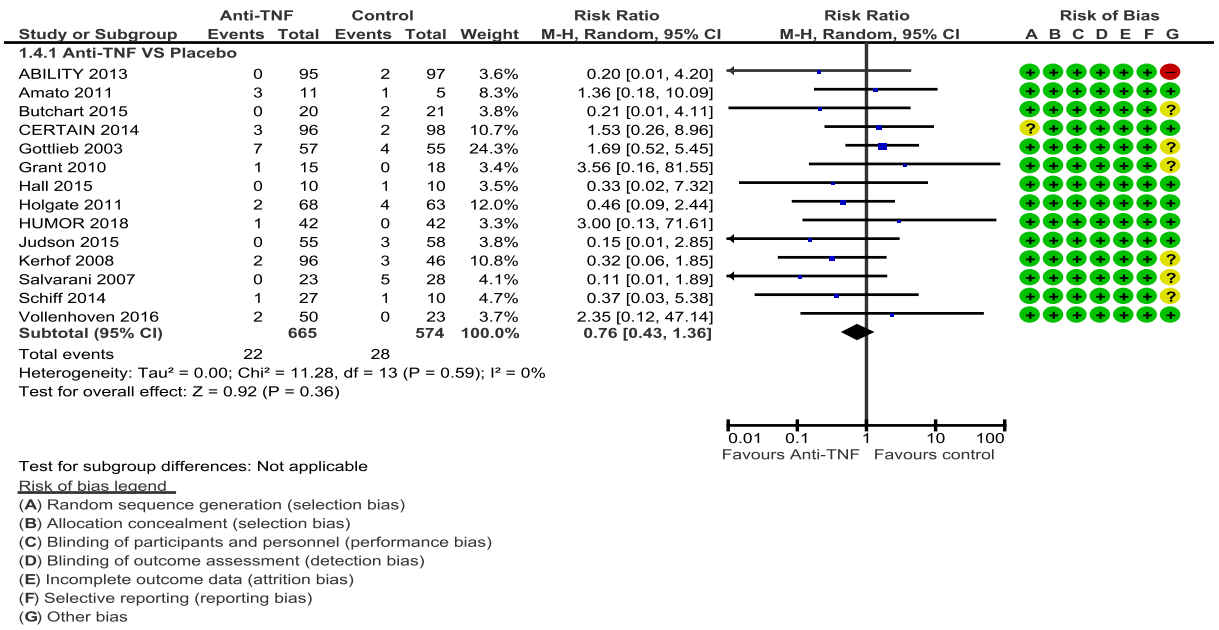

Figure 5-7 RE model for the association between the use of Anti-TNF drugs and the incidence of hypertension. Studies with more than 100 patients were excluded.

5.3.2 Subgroup analyses

The analysis was stratified by (1) comparator, (2) clinical population setting, and (3) duration of follow-up to assess the association between these factors and the effect of Anti-TNF on the risk of hypertension.

Table 5-4 Summary of subgroup analyses of Anti-TNF inhibitors impact on hypertension risk.

In the first subgroup analysis, only studies with active comparators were included in the analysis, while all studies were included in the remaining two subgroup analyses. Three studies compared Anti-TNF to MTX; one study did not estimate the effect size. The analysis included 1240 and 619 patients, respectively. The risk of hypertension was higher in Anti-TNF than in MTX (RR = 2.38, 95% CI 1.31; 4.32, P = 0.004). More than three-quarters of the subgroup meta-analysis weight was provided by Temp

study (85%). Compared to IL-6, the risk of hypertension was not significantly different between Anti-TNF and Anti-IL6 (RR = 0.91, 95% CI 0.56; 1.49, P = 0.71). No heterogeneity was observed between studies (I^2 = 0). The analysis included four studies with 2075 and 2257 patients in Anti-TNF and Anti-IL6 groups, respectively (See **Figure 5-8**).

Only one study included patients with hypertension at baseline, which is the Giles study. The remaining thirty-eight included patients with no hypertension at baseline, which were included in the meta-analysis, the analysis included 8498 and 4732 patients in Anti-TNF and the control group, respectively. A total of 313 and 159 events occurred in both groups, no association was observed between Anti-TNF and the risk of hypertension (RR = 1.26, 95% CI 0.99; 1.59, P = 0.06). Minimal heterogeneity was observed between studies (I^2 = 13%) (See **Figure 5-9**).

The follow-up duration was less than 2 years in thirty-six studies and two years or more in the remaining three studies. When the analysis was stratified by treatment duration, no association was observed between the use of anti-TNF and the risk of hypertension in patients who were followed up for less than 2 years (RR = 1.12, 95% CI, 0.90; 1.39, P = 0.31). Patients who were followed up for two years or more were statistically significant (RR = 2.32, 95% CI, 1.37; 3.93, P = 0.002). (I^2 = 0%) no heterogeneity was observed in both subgroups, respectively (See **Figure 5-10**).

Table 5-4 The Summary of a meta-analytical subgroup analysis by RE model demonstrates the effect of tumor necrosis factor inhibitors compared with control (placebo and active) on the risk of hypertension.

Subgroup analysis		**Studies**		**Participant**	**event**	**Hypertension Incidence (%)**		**RR (M-H, Random, 95% CI)**	**P value***	**I^2 (%)**
						Anti-TNF	Control			
Overall	RE	Placebo	30	9111	310	3.69	2.77	1.31 [1.00,1.73]	0.05*	2
		Active drugs	10	7312	175	2.30	2.49	1.14 [0.73,1.78]	0.56	38‡
Type of comparator	MTX		3	1859	51	2.98	2.26	2.38 [1.31,4.32]	0.004*	0
	Anti-IL6		4	4332	67	1.30	1.77	0.91 [0.56,1.49]	0.71	0
Clinical setting	No hypertension at baseline**		38	13230	472	3.68	3.36	1.26 [0.99,1.59]	0.06	13
Duration of follow-up	Less than two years**		36	12476	419	3.39	3.29	1.12 [0.90,1.39]	0.31	0
	Two years Or Longer**		3	3832	62	2.25	0.99	2.32 [1.37,3.93]	0.002*	0

† **list of definitions and abbreviations**: Cl: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant.; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity.;** Placebo and active drugs have been combined.

5.3.3 By type of comparator

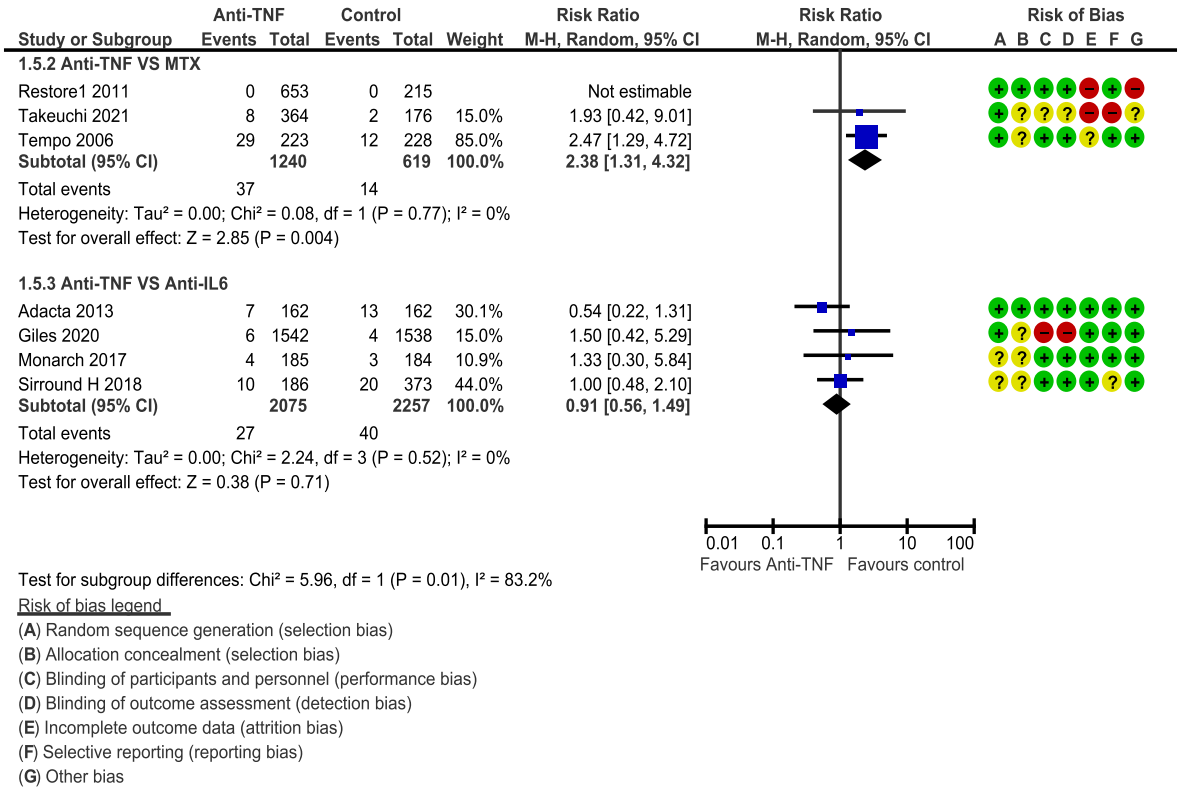

Figure 5-8 Subgroup analysis for the association between Anti-TNF drugs and the risk of hypertension. The analysis was stratified by the type of comparator.

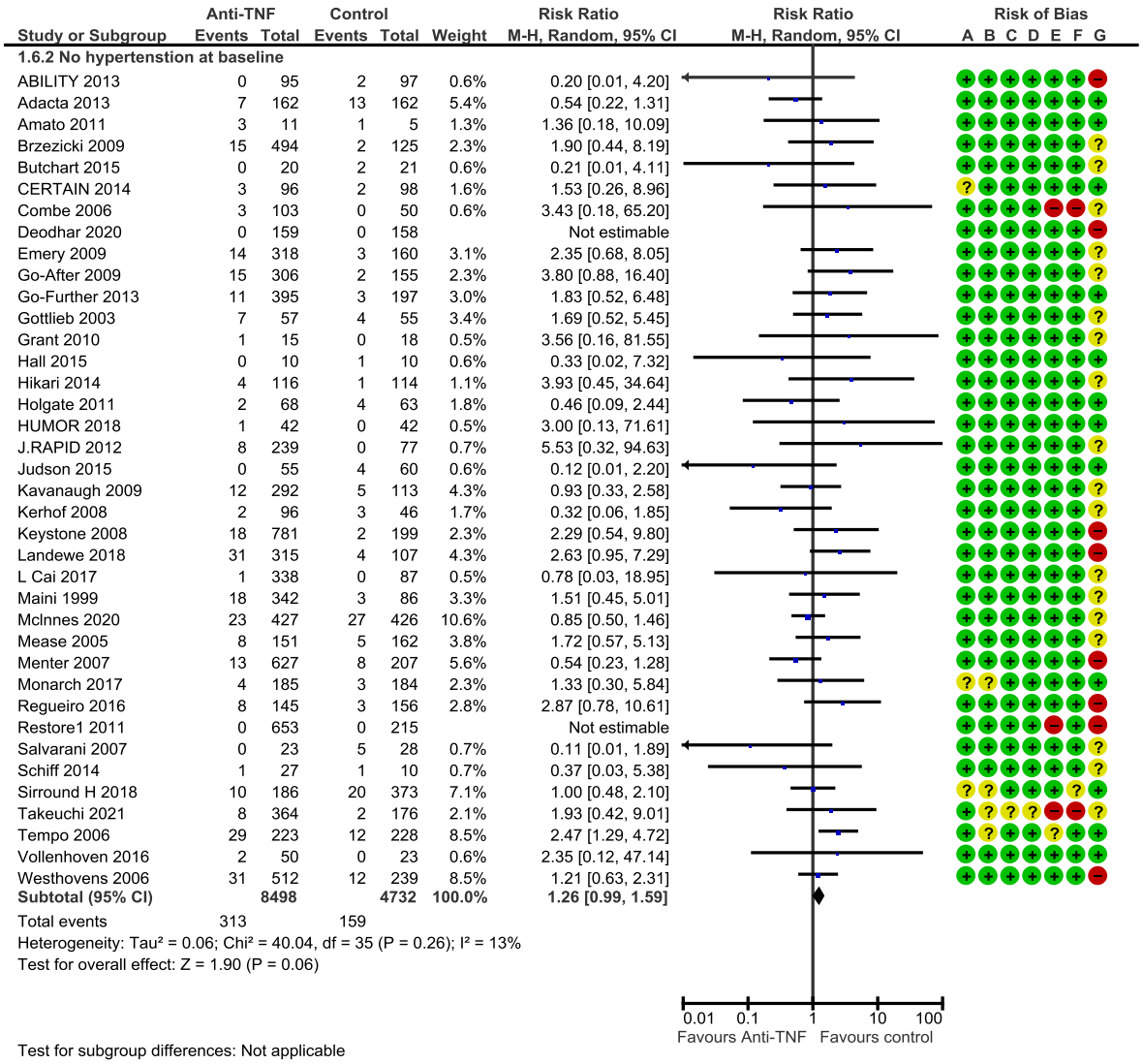

Figure 5-9 Subgroup analysis for the association between Anti-TNF drugs and the risk of hypertension. The analysis was stratified by clinical population setting. Placebo and active groups were combined.

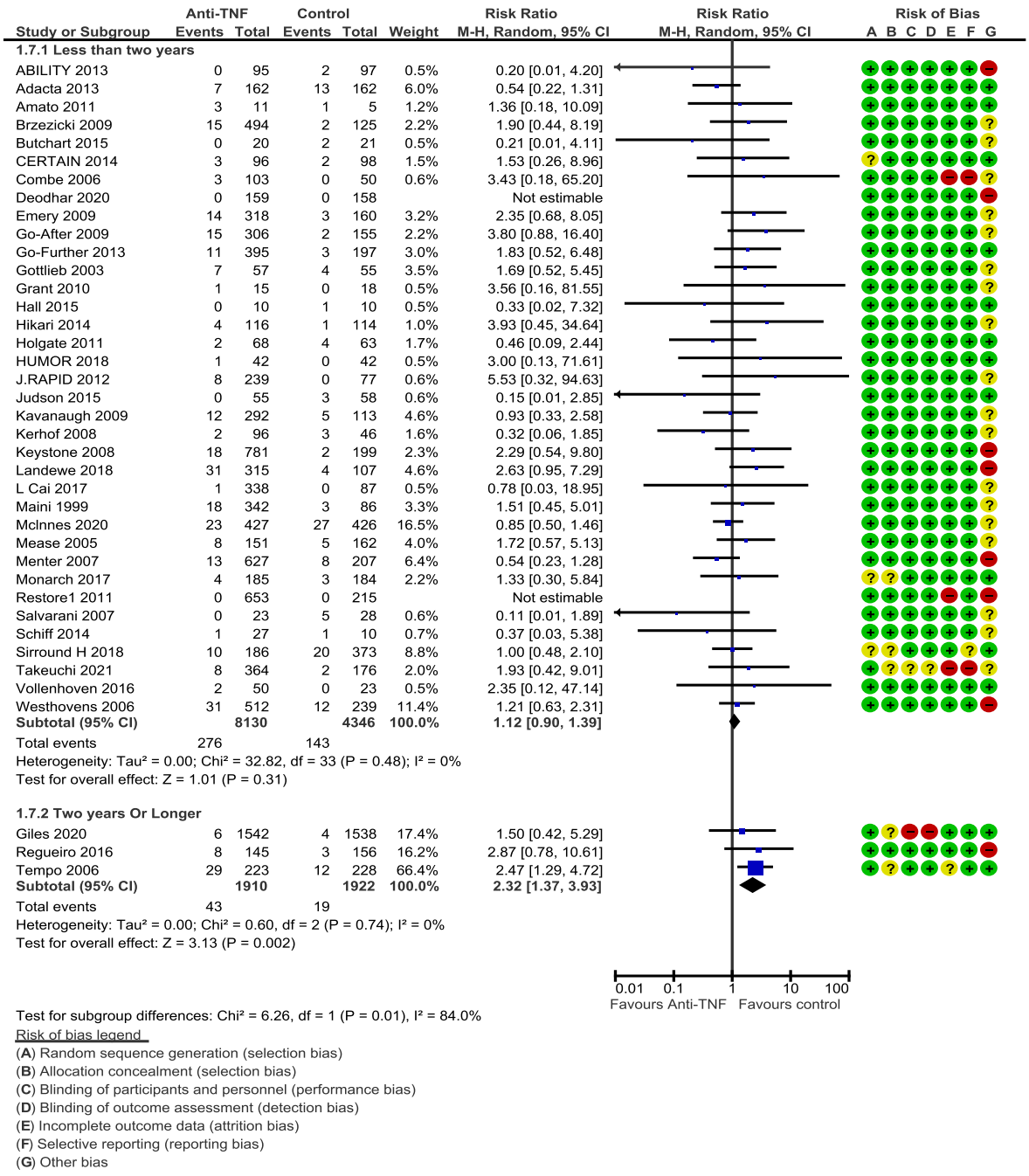

Figure 5-10 Subgroup analysis for the association between Anti-TNF drugs and the incidence of hypertension**.** The analysis was stratified by the duration of follow-up. Placebo and active groups were combined.

5.4 Discussion

The outcomes from the present study, after a comprehensive meta-analysis of the research hypothesis, have indicated that the inhibitors of TNF can increase the risk of hypertension when compared with the placebo. TNF plays a major role in maintaining the homeostasis of the human body. One of the most common roles, and a very important one, of these cytokines is in the host-defence mechanism of the immune system against various infections, such as bacteria, parasites and viruses. The TNF are very important, in that sense, but can be harmful when overproduced (Bradley, 2008). Hypertension is a low-grade inflammation-related disorder that is characterised by various types of proinflammatory cytokines. TNF is a type of proinflammatory cytokine associated with hypertension and some other abnormalities, such as renal injury (Mehaffey and Majid, 2017) . There are five main medications that can target TNF-receptors and so block the associated pathways; these are adalimumab, certolizumab, etanercept, infliximab and golimumab. A number of studies continue to try to understand the relationship of these inhibitors to hypertension. For example, a study by Fan et al. (2023) investigated the association of hypertension with some inflammatory cytokines by using bioinformatics; one of these was TNF. All of these medications are suspected to increase blood pressure. Conversely, other studies have suggested that these medications reduce the risk of hypertension, while some others state that they cause no increase in blood pressure and no risk of hypertension. TNF plays an important role in the initiation of inflammation by increasing the secretion of inflammatory mediators, which then leads to a number of inflammatory diseases (Oertle et al., 2002).In other research, Tran et al. (2009) indicated that etanercept can reduce the risk of hypertension. The present study, a comprehensive meta-analysis of findings on the effects of medications of Anti-TNF-Receptors on the risk of hypertension, indicates that these drugs may increase the risk of hypertension. Comparison of Anti-TNF-Receptors was with a placebo and active drugs. In comparisons with a placebo group, it was concluded that the risk of hypertension was elevated for participants on anti-TNF inhibitors; the results of this comparison were (RR = 1.31, 95% CI 1; 1.73, P = 0.05). No significant risk of hypertension was found between Anti-TNF-

Receptors drugs and some other active drugs; the results of this comparison were (RR = 1.14, 95% CI 0.73; 1.78, P = 0.56).Active drugs were stratified by a comparator in the analysis of two different subgroups. When Anti-TNF-Receptors were compared with Methotrexate, however, a higher risk of hypertension was seen to be associated with Anti-TNF-Receptors; the results of this comparison were (RR = 2.38, 95% CI 1.31; 4.32, P = 0.004). A number of factors explain the treatment gaps associated with MTX. For example, as described by Jawa et al. (2013), MTX non-adherence in patients with rheumatoid arthritis (RA) report a deterioration of symptoms and greater disability. When Anti-TNF-Receptors were compared with Anti-IL6, no difference was found in terms of the risk of hypertension between the two; the results of this comparison were (RR = 0.91, 95% CI 0.56; 1.49, P = 0.71). A number of previous studies support and justify these results. Their results vary with the type of study, the dose received and the state of the subjects. In addition, the final outcomes of the present study can wane with time. The study's main suggestion is that variations were observed in the risk of hypertension when Anti-TNF-Receptors were compared with a placebo and other active drugs. These results need re-investigation, with other factors being taken in account for complete justification. A study by Sriramula et al. (2013) , into the inhibition of the attenuation of angiotensin induced hypertension suggested that this effect of TNF, with its inhibitors, can be therapeutic in the management of hypertension and some other associated abnormalities that occur during treatment for various disorders. In this study, the main focus was on the maintenance of developed hypertension in the dysregulation of the RAS of the brain. Dolinger et al. (2020), in a study of the treatment of paediatric Crohn's disease and MIS-C and Corona Virus Disease-19, used one of the most popular antagonists of TNF-Receptor, infliximab. The major focus of this study was an evaluation of the effects of TNF-Receptors Inhibition in the control of the hypertension associated with inflammatory disorders such as Crohn's disease and MIS-C in case of children related to Corona Virus. Treatment with infliximab led to a reduction in associated abnormalities such as blood pressure, fever and tachycardia within hours.

In a study done by Elmarakby et al. (2008) assessed the Renal Injury in DOCA-Salt Hypertensive Rats can be treated by using Etanercept (TNF-alpha-inhibitors). The main focus of the study was on the slowing down the progression of renal damage and hypertension in Angiotensin-II-Salt Sensitive Hypertension. The hypothesis of the study was that the Etanercept (inhibitor of TNF) can treat renal inflammation by avoiding the risk of hypertension. The results suggested that TNF-alpha causes increase risk of hypertension which can be well inhibited by Etanercept, this study indicates that TNF-alpha-inhibitors can reduce the levels of hypertension. Kusakari et al. (2015) suggested that adalimumab and infliximab, when used to treat psoriasis complicated with renal damage and hypertension. These drugs were not seen to reduce blood pressure. The authors suggested, however, that the results needed further investigation, to provide them with a reasonable and clear justification. Khan and Scott (2011) suggested that certolizumab (a TNF-Receptor-Antagonist), when used in combination with methotrexate, could improve rheumatoid arthritis outcomes by slowing its progression. Certolizumab was seen to increase some adverse events, including some serious infections, such as respiratory tract infections, nasopharyngitis and hypertension. Since hypertension is considered to be one of the most common serious adverse effects of this drug, this is an indication that certolizumab can increase the risk of hypertension during treatment of rheumatoid arthritis or some other inflammatory disorder.

Thus, it can be concluded that the inhibition of TNF by adalimumab, certolizumab, etanercept, golimumab and infliximab has different effects on blood pressure levels. Some of them can increase the risk of hypertension, while others can decrease it , some medications have not been associated with any hypertension risk. Several factors influenced this outcome. The first of these factors was the comparison made between Anti-TNF-Receptors and other active drugs. The results of this comparison showed no difference. A previous study of the drug certolizumab indicated that this drug can increase the risk of hypertension.

The present comprehensive meta-analysis, involving a comparison of Anti-TNF-Receptors with a Placebo Group, has shown that Anti-TNF-Receptors had a higher risk of hypertension than a placebo.

Information collected from previous studies has indicated that there is no risk of hypertension associated with these drugs, but most of the studies have recommended further investigation, given that the underlying mechanisms remain unclear. Another justification of this outcome might be that there can be something uncommon in those subjects due to which results cannot be similar. These factors might include patients' age, gender or their state of health. Taking these factors in account will entail a redesign and a further implementation of the research. However, most of the comparisons in the our study and the present study suggests that there can be a risk of hypertension, in spite of most previous studies stating that there is no such risk if Anti-TNF-Receptors are used at standard doses.

5.5 Conclusion

The main focus of the study is on the effects of the featured medications on hypertension. From the results of the study and those of some previous investigations, it can be concluded that all of the medications have different effects. Some can increase the risk of hypertension, while some do not, and there are some medications that do not have any kind of effect on blood pressure. Some previous studies have indicated that all the inhibitors of TNF-Receptors can decrease blood pressure levels, with one more related study showed the similar effects. Most previous studies have suggested that further investigations were needed, because of uncertainty about the underlying mechanisms that produced the observed results. Some another justification can be given here with some other previous and our own first comparison. In a study it was concluded that Anti-TNF-Receptors may increase the risk of hypertension, and the results of the current study have shown that these inhibitors are on the edge of increasing the risk of hypertension than a placebo, even if this risk is increased by just a small amount. Moreover, after excluding studies with a high risk of bias, the results of anti-TNF were compared to a placebo. The estimate from the RE model showed that the risk of hypertension was not statistically significant. Also, anti-TNF was compared to other active drugs; however, the risk of hypertension was not significantly different between groups.

5.6 Strengths and Limitations

There are both strengths and limitations of the current study, and they have affected the final outcomes of the work, either directly or indirectly. In terms of the strong points of the study, the combination of information collected from past literature and the results of the study itself has provided some robust and valid findings. The quality of the meta-analysis carried out was improved by consideration of unpublished data from Hall, Regueiro, Amato, Vollenhoven, Takeuchi, Judson, Deodhar, Schiff, Landewe, J.rapid and Ability.

There were three main limitations of the research, which had some negative impacts. The first limitation is that there were very few studies that addressed the hypothesis of the present work and most of the work reviewed did not have clear results, which made it difficult to deduce relevant outcomes. To add to the lack of quality data, most previous research studies admitted that further investigation was required. None identified the precise mechanism that had produced the observed results. It should be stated, however, that the present investigation is rare and that the outcomes of the meta-analysis carried out offer new, potentially beneficial information that can be used in the future. Another limitation of the work is that, even with so many studies on the relationship between various medications and hypertension, none of them focused mainly on hypertension. Furthermore, the sample size in most of the studies was small, except for the studies by Keystone and Giles, which had slightly larger samples. A considerable sample size is required for a more precise estimate of treatments' effects.

The limitations outlined above collectively entail a lack of complete and detailed information with which to justify the hypothesis of the current research. There were other limitations, but they did not affect the accuracy of the study's results; they included time constraints, the lack of data and deadlines that required the contacting of authors in order to obtain further information. The strengths and limitations of the study have influenced the outcomes of the work in a positive and negative manner. Overall, however, the outcomes are logical and accurate.

6. The association between Interleukin-17 inhibitors and risk of hypertension

6.1 Introduction

Interleukins are proinflammatory cytokines in IL-17 family, form a group of six proteins, ranging from Interleukin 17A to Interleukin 17F. The main sources of these cytokines are Th17 generators such as the mast cells and neutrophils (Iwakura et al., 2011).The main objective of this study is to analyse the extent of any hypertension that may occur due to Interleukin-17 inhibitors, in particular Ixekizumab, Secukinumab, and Brodalumab. Both Secukinumab and Ixekizumab were approved by the FDA in 2016, while Brodalumab was approved in 2017m(Berry et al., 2022).

Secukinumab is a fully human monoclonal antibody that specifically targets and neutralises Interleukin-17 (Pinter et al., 2020).Secukinumab binds to IL-17 receptors, being one of the most recent biologic therapies for psoriasis treatment. Secukinumab possess high affinity for Interleukin-17 A and has thus been licensed to treat psoriatic arthritis and plaque psoriasis, outperforming the two most commonly prescribed drugs in this area, Ustekinumab and Guselkumab due to offering longer efficacy ,It has also been recommended for psoriasis treatment in humans by the European Medicine Agency's Committee for the Medicinal Products.The most common adverse drug reactions (ADR) for this drug are relatively minor, including reactions at the site of injection, candida infections, and nasopharyngitis (Sanford and McKeage, 2015).

Another USFDA approved monoclonal antibody, Ixekizumab, also act as an inhibitor of Interleukin-17, and this can be used to treat plaque psoriasis in adults, being mainly used for those who have ceased responding to therapies such as topical and systemic drugs (Genovese et al., 2020).

6.1.1 Interleukin-17-Inhibitors' Mechanisms of Action

Interleukin-17-inhibitors act by binding to the receptors of Interleukin-17 and blocking them, as shown in **Figure 6-1**. The immunopathology thus developed can be discussed briefly by identifying the key mediators of the relevant inflammatory diseases and examining how Interleukim-17-inhibitors target them. Many such disorders involve hyper-proliferation of the keratinocytes, a process that interferes with their terminal differentiation. The hyper proliferation of keratinocytes can thus cause poor adhesion of the stratum corneum, leading to plaque formation. Keratinocytes thus appear to drive immune-mediated inflammatory responses, which can be acute as well as chronic. However, the exact mechanism of this process unknown. The development of the relevant diseases certainly involves an interplay between environmental, genetic, and other factors such as injuries, viral or bacterial infections, stress, smoking, alcohol abuse, and obesity (Bos et al., 2005).

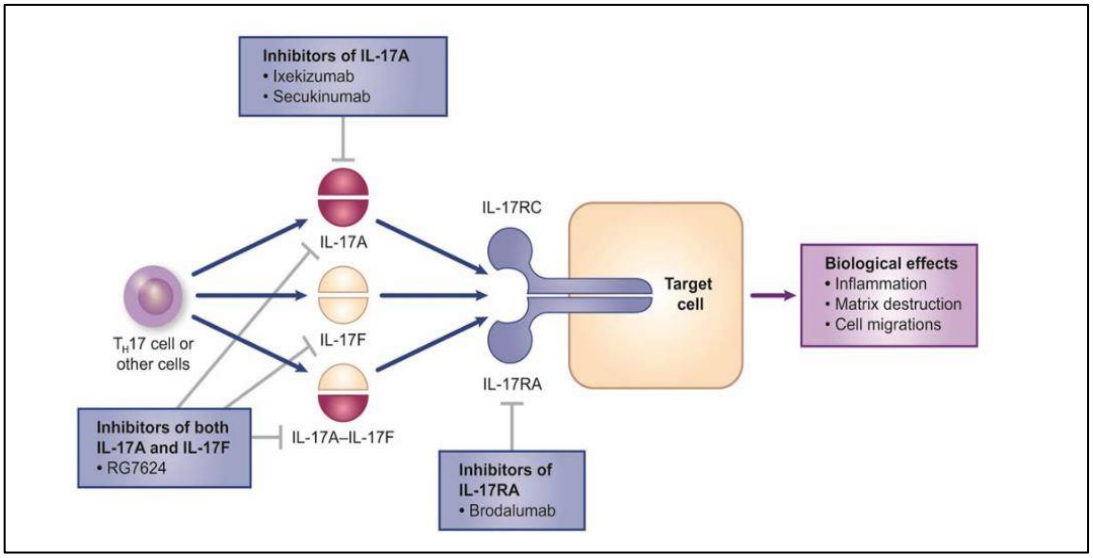

Figure 6-1 Interleukin-17-Inhibitors Targeting IL-17 Signalling Pathway

Adapted from Gaspari and Tyring (2015).

The targeting of Interleukin-17 signalling pathways requires identification of the subunits of the receptors of Interleukin-17 present on various cells, including endothelial cells, dendritic cells, dermal fibroblasts, and keratinocytes. Monoclonal antibodies such as Ixekizumab, Secukinumab, and Brodalumab target these cytokines to prevent inflammatory mediated effects

by neutralising Interleukin-17. Ixekizumab and Secukinumab create inhibition of Interleukin-17A with respect to its receptor, while Brodalumab acts as a type of antibody, binding to the receptors of Interleukin-17RA and blocking any signalling through its receptor (Gaspari and Tyring, 2015).

6.1.2 The hypothesis from basic science

Previous investigations on the effect of Interleukin-17-inhibitors on experimental animals (pre-clinical studies) offer justification for further research in this area. In terms of the effects of various medications on hypertension, however, some previous experimental findings have offered different results. Some of these are thus shown in **Table 6-1.**

Table 6-1 Selected previous pre-clinical studies

Study	Study design	Animals used	Follow-up Period	Interventions	Results and Summary	Reference
Spironolactone Decreases DOCA–Salt–Induced Organ Damage by Blocking the Activation of T Helper 17 and the Downregulation of Regulatory T Lymphocytes	Lab Test.	rats	8-28 days	Anti-IL17	Improved and reduced hypertension	(Amador et al., 2014)
Inhibition of Interleukin-17A, But Not Interleukin-17F, Signalling Lowers Blood Pressure, and Reduces End-Organ Inflammation in Angiotensin II–Induced Hypertension	Lab Test.	Mouse model	28 Days.	Anti-IL 17 led to a reduction in blood pressure.	Adjunct decrease in blood pressure.	(Saleh et al., 2016).

6.1.3 Rationale for the current study

Multiple clinical studies have already studied the effects of various inhibitors on hypertension. Randomised double blinded controlled period study investigated the efficacy and safety of Ixekizumab in the treatment of Psoriatic Arthritis, which revealed that Ixekizumab actually reduced the observed hypertension during such treatment (Nash et al., 2017). Eichhoff (2020) also suggested that when Secukinumab was used to treat Psoriasis, it led to hypertension when the drug was replaced by Cyclosporine.

Table 6-2 illustrates the various clinical studies conducted to investigate the effects of Anti-IL-17.

Table 6-2 Selected previous clinical studies

Study	Subjects	Follow up Period	Intervention	Comparators	Results/ Summary
(Huang et al., 2019a). Efficacy and safety of Secukinumab in active rheumatoid arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis of phase III randomized controlled trials.	1,292, Rheumatoid Arthritis.	24 weeks	Secukinumab 75 mg and 150 mg	Placebo.	No significant difference in the AEs of the Placebo and Secukinumab, hypertension
(Xiong et al., 2015). Efficacy and safety of Secukinumab in the treatment of moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials.	3,213, Plaque Psoriasis	-	Secukinumab	Placebo.	No statistical difference in the AEs of the placebo and Secukinumab, including hypertension.
(Wu et al., 2019). Meta-analysis of IL-17 inhibitors in two populations of rheumatoid arthritis patients: biologic-naive or tumour necrosis factor inhibitor Inadequate responders	2,499, Rheumatoid Arthritis.	-	Interleukin-17-inhibitors	Placebo.	When used to treat rheumatoid arthritis, do not increase the incidence of hypertension or any other cardiovascular events.

6.2 Methodology

6.2.1 Search strategy and eligibility criteria

A comprehensive description of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

6.2.2 Data extraction

The initial search using the search strategies detailed in the **Appendix A.** yielded 137 articles, with information obtained from various bibliographic and non-bibliographic database sources. The PRISMA study flow diagram in **Figure 6-2** summarises the identification of the research objects.

After removing duplicates, the remaining 95 citations or abstracts were assessed using the predefined inclusion criteria. At that point, 62 articles were eliminated based on the title and abstract review process, removing almost 85% of the total based on PICOS criteria. Of the 33 publications that remained, thirteen RCTs were eliminated after full-text screening for reasons which are described in **chapter 3,Table 3-1**. Ultimately, twenty trials, with a total of 8,619 patients enrolled, were thus selected for qualitative and quantitative synthesis to form the final review. The excluded and included studies have been described in the methodology sections.

6.2.3 Excluded studies

The thirteen publications excluded after an extensive eligibility check of the full text included two trials (GERDES and PINTER) that reported different outcomes, and which did not mention hypertension (HTN). One study (SCULPTURE) was removed for using a cohort design, while the RESZKE study was excluded as being a simple review. The most commonly excluded types of studies, however, were those which had used Anti-17 in both arms, along with abstracts, notes of annual meetings, and conference proceedings.in **chapter 3,Table 3-1** summarises the reasons for elimination for each piece.

6.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.

Sensitivity analyses were completed after the exclusion of trials with [1] poor methodological qualities; [2] small sample sizes of less than 100 total participants; and [3] excessively large sample sizes.

Subgroup analyses for Anti-IL17 were performed as follows: (1) comparator drugs; (2) duration of follow-up.

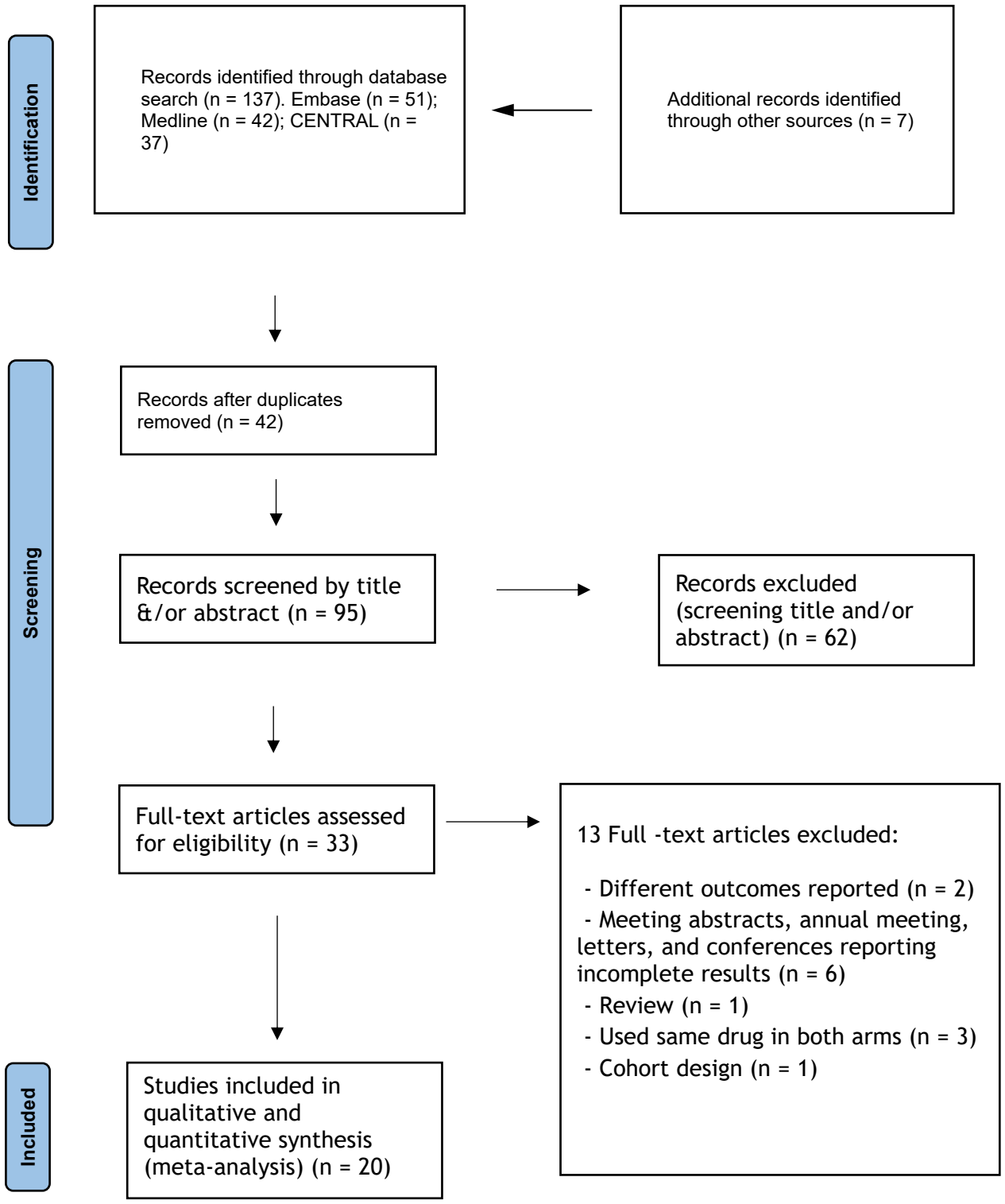

Figure 6-2 PRISMA Study flow diagram

6.3 Results

In total, twenty eligible Anti-IL17 trials were identified. These studies incorporated data from 8,619 patients, with an average follow-up period of 1.36 years (ranging from three to thirty months). The average patient age across all trials was forty-five years old.

The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

All of the included studies were published after 2012, with the most recent studies included being published in 2020 and 2021 (Huang, Mclnnes, Deodhar, and Clarity).

The majority of the included studies were published between 2015 and 2018.

J.Mease, Juncture, Langley, and Paveika all published their findings in 2015. The same interleukine-17 inhibitor was used in both the J.Mease and Juncture studies, but at different dosage strengths: both were phase 3 clinical trials, though they had different follow-up durations, with 24 weeks used in the J.Mease study. In the Langley study, the intervention was Ixekizumab, with 142 patients with long-term plaque psoriasis offered subcutaneous injections of 10, 25, 75, and 150 mg of Ixekizumab in a phase 2 trial. A further 252 patients had rheumatoid arthritis and were responding poorly to methotrexate; these patients received subcutaneous injections of Brodalumab with different strengths (70 mg, 140 mg, and 210 mg).

In the A.Papp study, published in 2013, which was the oldest trial included in this meta-analysis, Secukinumab at different strengths (25 mg, 75 mg, and 150 mg) was compared to a placebo. Both the Clarity and Paul studies used the same comparator, Ustekinumab at 45 mg or 90 mg, with different interleukine-17 inhibitors, namely Secukinumab 300 mg in the Clarity study and Ixekizumab 80 mg in the Paul study. Both studies had the same 52-week follow-up duration and were phase three clinical trials.

Seventeen studies compared Anti-IL17 with a placebo (Papp, Braun, Deodhar, Dokoupilova, Huang, Future 5, Juncture, Measure 4 , Lagley, J Mease, Spirit-P2, Papp,

Paveika, Rich, Ryan, and Tahir) with all of these reporting hypertension as an adverse event.

Three studies compared Anti-IL17 to active controls, including other anti-TNF agents and Ustekinumab; Only ustekinumab was divided into subgroups for the purpose of analysis in this study (see **Figure 6-8**).

Most studies employed a double-blind design except for Papp and Ryan, which used double-blind and open-label designs. Papp used a double-blind design in all groups in the first year; then, at the end of year one, when only one group only still continued to use Brodalumab 210 mg/Q2W, the study switched to an open-label design until week 120. Ryan used a double-blind design in both arms in the first year, switching to an open-label design.

The follow-up study periods ranged from three to thirty months. All study participants were adults, with a mean age of forty-five years old. There were no specifically single-sex studies, though the proportion of male and female participants differed from study to study.

The anti-interleukin 17 agents used covered a wide range of drug treatments, with different studies using various different drugs such as Ixekizumab, Secukinumab, and Brodalumab (which were used as keyword search terms).

Most studies involved participants diagnosed with psoriatic arthritis, while some studies also incorporated those diagnosed with rheumatoid arthritis, such as Dokoupilova, Paveika and Tahir. Two studies further included patients diagnosed with ankylosing spondylitis; these were Braun and Huang. Only one study, Deodhar, incorporated patients diagnosed with axial spondyloarthritis. Further details of participants' background conditions are given in **Table 6-3.**

Table 6-3 The underlying disease of each trial

Trial	Background condition	Trial	Background condition
A.Papp 2013	plaque psoriasis	Spirit-P2 2017	psoriatic arthritis.
Braun 2017	ankylosing spondylitis	Papp 2014	plaque psoriasis
Deodhar 2021	Axial Spondylarthritis	Paveika 2015	rheumatoid arthritis
Dokoupilova 2018	rheumatoid arthritis	Rich 2013	plaque psoriasis
Huang 2020	ankylosing spondylitis	Ryan 2018	plaque psoriasis
J.Mease 2015	psoriatic arthritis.	Tahir 2017	rheumatoid arthritis
Juncture 2015	plaque psoriasis	Clarity 2021	plaque psoriasis
Achilles 2022	Spondylarthritis	Mclnnes 2020	psoriatic arthritis.
Measure 4 2018	Psoriatic arthritis	Paul 2019	plaque psoriasis
Lagley 2015	plaque psoriasis	Future 2018	psoriatic arthritis.

Seventeen studies were included in the meta-analysis comparing Anti-IL17 use to a placebo. The meta analysis thus included 4,391 and 1,972 patients in the treatment and placebo arms, with 133 and 46 events, respectively. The results were not statistically significant in any of the seventeen studies at the 95% confidence interval for relative risk. In the random-effects model, the highest weights were assigned to Future 5 and Tahir (28.3% and 10.3%, respectively) due to the larger sample sizes in these two studies, which were assumed to offer higher precision. Three studies included in the meta-analysis compared Anti-IL17 to other active drugs, giving groups of 1,111 and 1,145 patients, respectively. The numbers of events in both arms were 51 and 60, respectively, and the results (RR) were not statistically significant. The highest weight was assigned to the Mclnnes study (45.5%) , while the Paul study was assigned the lowest weight (19.1%).

The pooled estimate from the random effects meta-analysis showed that the risk of hypertension was not significantly different between Anti-IL17 and a placebo drug (RR = 1.09, 95% CI 0.75, 1.58, P = 0.65). Similarly, the risk of hypertension was not significantly different between Anti-IL17 and other active drugs (RR = 0.89, 95% CI 0.60, 1.31, P = 0.54). Low heterogeneity was observed between studies comparing Anti-IL17 to a placebo drug (I^2 = 9, Cochrane Q test P = 0.34), as well as between

studies that compared Anti-IL17 to other active drugs (I^2 = 9, Cochrane Q test P =0.33) (See **Figure 6-3**).

The pooled estimate from the fixed effects meta-analysis (**Figure 6-4**). However, the results showed that the number of hypertension events was higher in the anti-IL17 group compared to the placebo group, but the difference was not statistically significant (RR = 1.25, 95% CI 0.90, 1.72, P = 0.19), though the risk of hypertension remained not significantly different between Anti-IL17 and the other active drugs (RR = 0.89, 95% CI 0.62, 1.28, P = 0.52). Low heterogeneity was observed between studies comparing Anti-IL17 to both a placebo drug (I^2 = 9%, Cochrane Q test P = 0.34) and to other active drugs (I^2 = 9%, Cochrane Q test P = 0.33).

Appendix D, Figure D-3 shows the distribution of the 15 studies in a funnel plot. Although there is a missing study at the bottom left of the plot, no outlier can be observed and the plot appears fairly symmetrical.

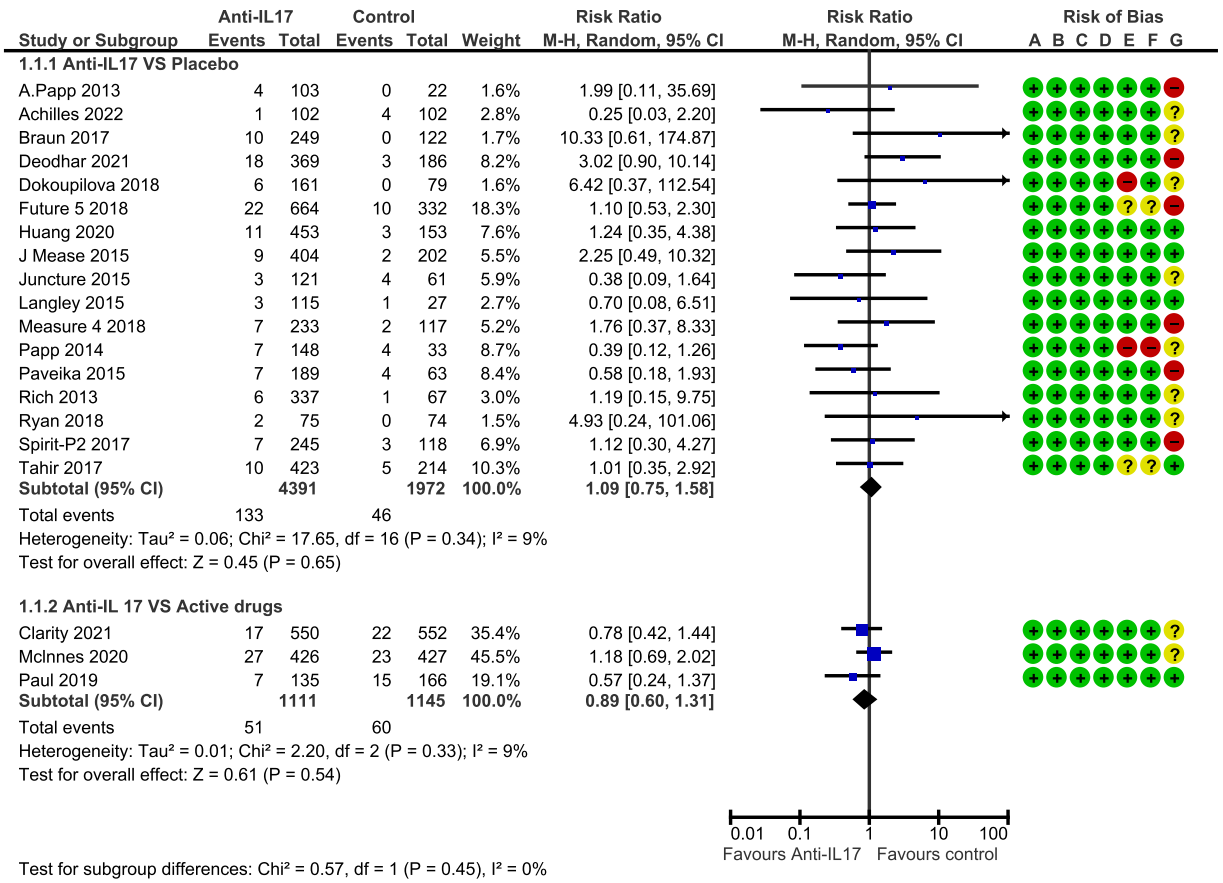

Figure 6-3 Random effects model for the association between Anti-IL17 drugs and the risk of hypertension.

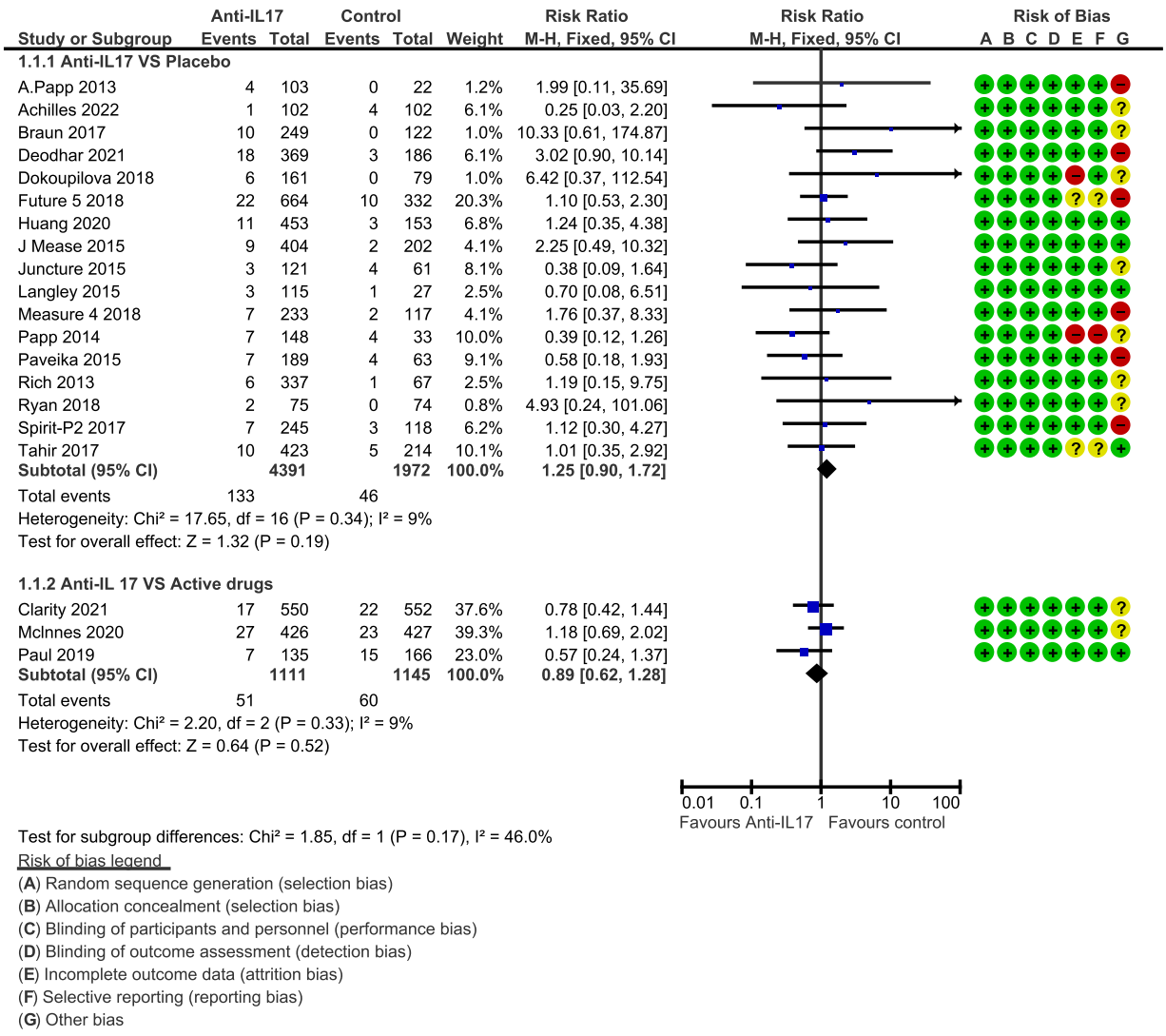

Figure 6-4 Fixed effects model for the association between Anti-IL17 drugs and the risk of hypertension.

6.3.1 Sensitivity analyses

The results of the original RE model meta-analysis did not change when the Ryan study was excluded (RR = 1.06, 95% CI 0.73; 1.55, P = 0.74), indicating that the results are robust to the exclusion of studies with small sample sizes. That analysis included 4,316 and 1,898 patients in Anti-IL17 and the control groups, respectively, with low heterogeneity observed between studies (I^2 = 10%,P = 0.34) (See **Figure 6-5**).

As **Figure 6-6** shows, Five studies (A.Papp, Deodhar, Future 5, Spirit-P2, and Paveika) were then excluded from the placebo subgroup due to high risk of bias, as their samples were relatively large as compared to their study periods, which increases the risk of data accuracy issues. After this exclusion, the risk of hypertension was not found to be significantly different between Anti-IL17 and the placebo group (RR = 0.98, 95% CI 0.55; 1.78, P = 0.96). That analysis included 2,588 and 1,134 patients in the Anti-IL17 and placebo groups, respectively, and low heterogeneity was observed between studies (I^2 = 24%,P = 0.22).

One study (Future 5) was excluded from the placebo group specifically due to large sample size. In the active subgroup comparison, one study was excluded, though the estimates and the interpretation of results did not change. In the placebo subgroup analysis, the risk of hypertension was not seen to be significantly different between Anti-IL17 and the placebo (RR = 1.10, 95% CI 0.71; 1.70, P = 0.67). That analysis included 3,727 and 1,640 patients, respectively, in each group, with events occurring in 111 and 36 patients. Low and non-significant heterogeneity was also observed between studies (I^2 = 16%,P = 0.27). When Anti-IL17 was compared to other active drugs, no significant difference was observed (RR = 0.89, 95% CI 0.45; 1.77, P = 0.75), indicating the robustness of the initial results. Again, low heterogeneity was observed between studies (I^2 = 47%,P = 0.17)(See **Figure 6-7**).

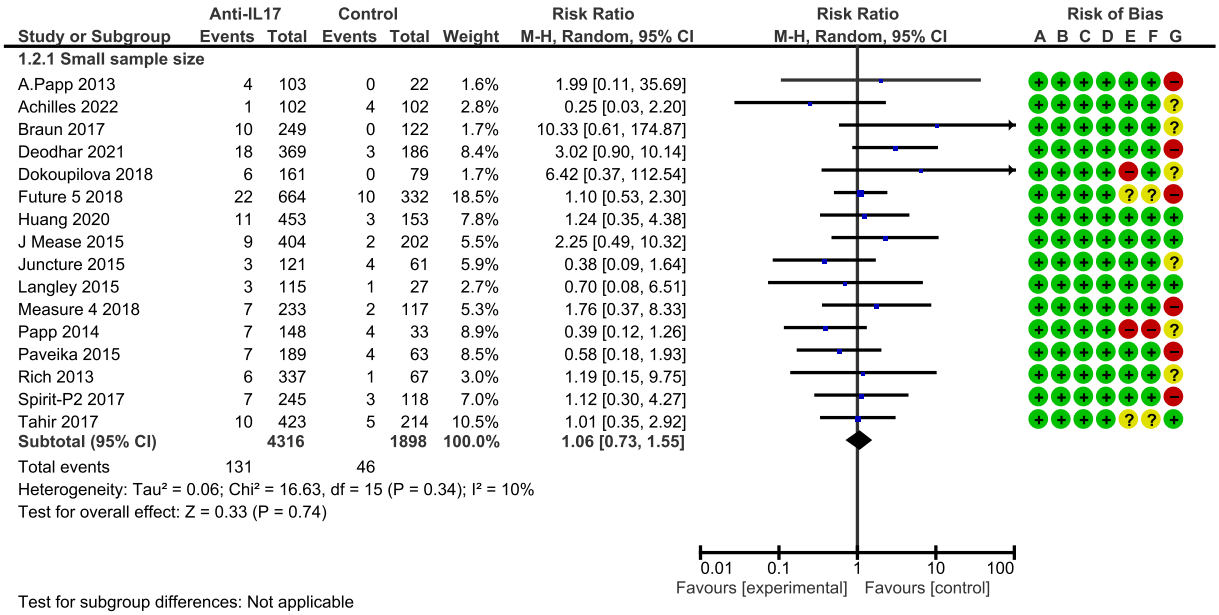

Figure 6-5 Sensitivity analysis for the association between Anti-IL17 and risk of hypertension (excluding studies with a small sample size)

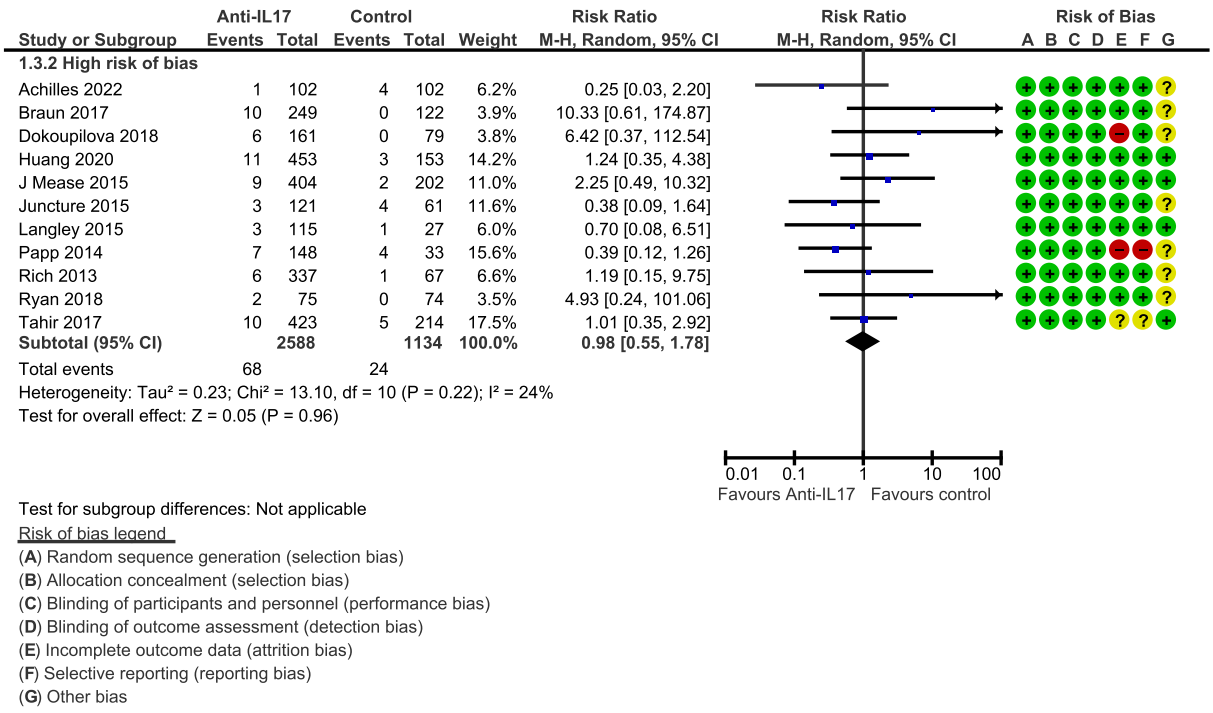

Figure 6-6 Sensitivity analysis for the association between Anti-IL17 and risk of hypertension (excluding studies with a high risk of bias)

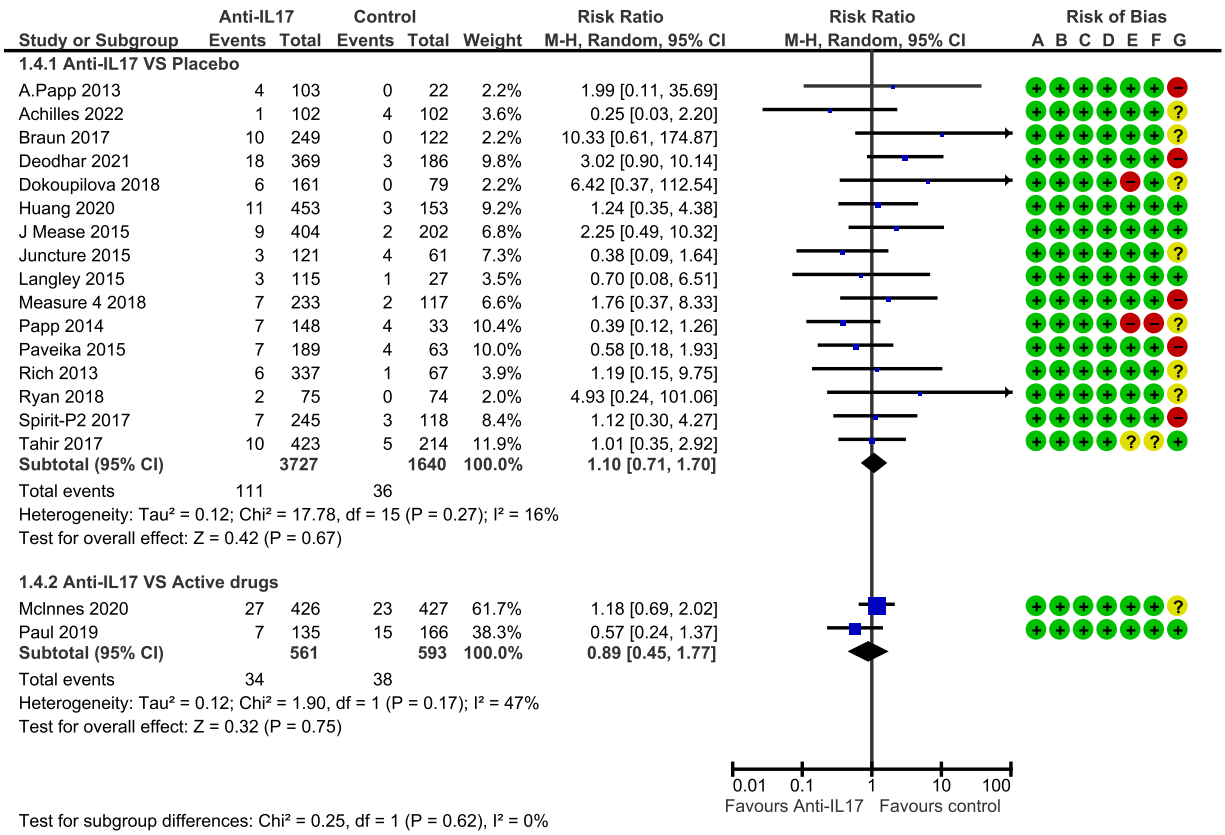

Figure 6-7 Sensitivity analysis for the association between Anti-IL17 and risk of hypertension (excluding studies with a large sample size)

6.3.2 Subgroup analyses

Table 6-4 Summary of subgroup analyses of Anti-Interleukin 17 inhibitors impact on hypertension risk.

Two studies compared Anti-IL17 to Ustekinumab, which showed that the risk of hypertension did not vary between groups (RR = 0.7, 95% CI 0.42; 1.16, P = 0.17). However, no heterogeneity was observed between studies (I^2 = 0,P = 0.58). (see **Figure 6-8**).

The follow-up duration was under two years in seventeen studies and two years or more in the remaining three studies. When analysis was stratified by treatment duration, no association was observed between the use of Anti-IL17 and the risk of hypertension in patients followed up for under two years (RR = 1.00, 95% CI 0.77; 1.30, P = 0.99) and those followed up for two or more years (RR = 1.41, 95% CI 0.23; 8.72, P = 0.71). For the first subgroup, 4,872 and 2,845 patients were included in Anti-IL17 and control groups, respectively, with no heterogeneity observed between studies (I^2 = 0,P =0.58).For the second subgroup, 630 and 272 patients were included in the Anti-IL17 and the control groups, respectively; however, in this case, substantial heterogeneity was observed between studies (I^2 = 70,P = 0.04). (see **Figure 6-9**).

Table 6-4 Summary of meta-analytical subgroup analysis using an RE model to demonstrate the effect of Interlukine-17 inhibitors as compared with controls (placebo and active) with respect to the risk of hypertension

Subgroup analysis		**Studies**		**Participant**	**event**	**Hypertension Incidence (%)**		**RR (M-H, Random, 95% CI)**	**P value***	**I^2 (%)**
						Anti-17	Control			
Overall	RE	Placebo	17	6363	179	3.02	2.33	1.09 [0.75,1.58]	0.65	9
		Active drugs	3	2256	111	4.59	5.24	0.89 [0.60,1.31]	0.54	9
Type of comparator	Ustekinumab		2	1403	61	3.50	5.15	0.70 [0.42,1.16]	0.17	0
Duration of follow-up	Less than two years**		17	7717	260	3.28	3.51	1.00 [0.77,1.30]	0.99	0
	Two years Or Longer**		3	902	30	3.80	2.20	1.41 [0.23,8.72]	0.71	70

† **list of definitions and abbreviations**: Cl: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant.; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity.;** Placebo and active drugs have been combined.

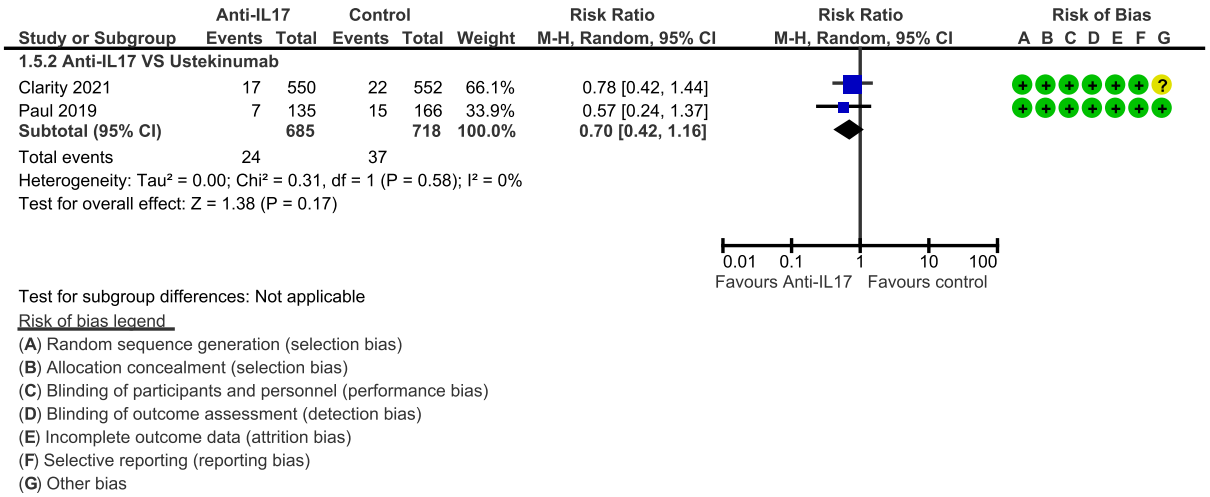

Figure 6-8 Subgroup analysis for the association between Anti-IL17 and the risk of hypertension (The analysis was first stratified by comparator type)

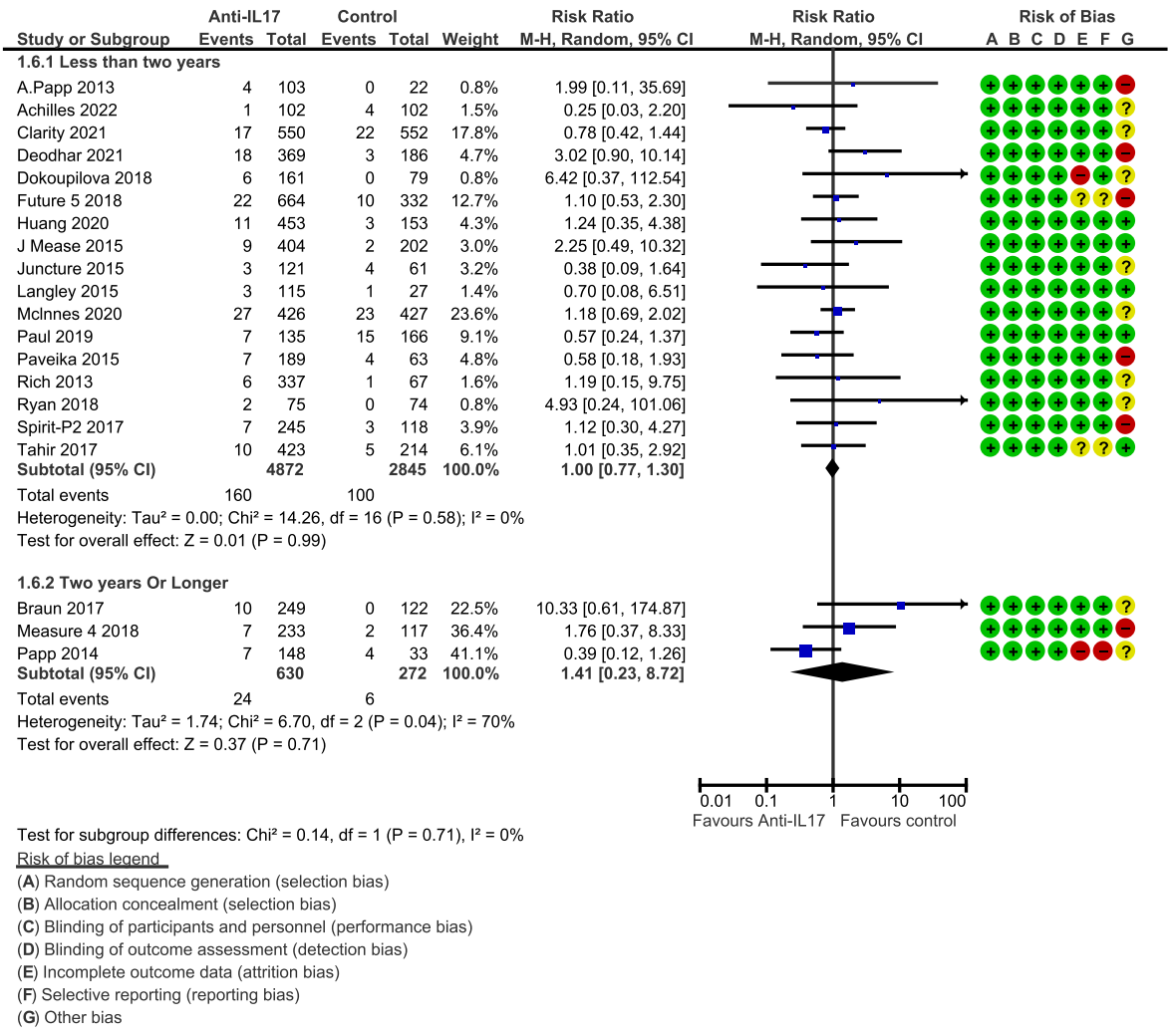

Figure 6-9 Subgroup analysis for the association between Anti-IL17 and the risk of hypertension (All analysis was then stratified by duration of treatment, with the placebo and active comparator arms were combined for this purpose)

6.4 Discussion

The outcomes from the current study indicate that Anti-IL17 inhibitors do not increased risk related to hypertension. Interleukin-17 plays a major role in various physiological abnormalities as a type of cytokine that shows strong synergies with other cytokines such as TNF-α which modulate inflammatory response (Ruddy et al., 2004). Madhur et al. (2010) first reported Interleukin-17 as maintaining Angiotensin-II induced hypertension and since then, three agents that can target Interleukin-17 by blocking the associated pathways have been identified. These are Secukinumab, Brodalumab, and Ixekizumab, though a great deal of research is still ongoing with respect to the relevant pathways (Bai et al., 2019). All of these drugs are suspected to cause the risk of hypertension; however, other researchers contend that these inhibitors do not cause any risk. The overall evidence examined in the current review suggests that there is no association between Interleukin-17-inhibitors and the risk of hypertension. Pinter et al. (2020) indicated that patients treated with Secukinumab had a reduced risk of hypertension. The findings of the current research suggest that Interleukin-17 inhibitors, when compared with placebos and other active drugs, showed no alteration in either direction in the risk of hypertension. Such drugs are mainly used to treat diseases such as psoriasis, arthritis, and other inflammation-related conditions.

The comprehensive meta-analysis findings with respect to Interleukin-17 inhibitors in terms of the risk of hypertension thus indicate that these drugs carry no particular risk associated with hypertension. Interleukin-17-inhibitors were compared to placebos and active drugs, and the pooled estimation of random effects did not show any substantial differences in the risk of hypertension (RR = 1.09, 95% CI 0.75, 1.58, P = 0.65). In a similar manner, the risk of hypertension was not observed to be changed in a comparison between Interleukin-17-Inhibitors and active drugs (RR = 0.89, 95% CI 0.60, 1.31, P = 0.54).

A number of previous studies support these results and can be used to justify them, though such results vary with the type of study done, and in particular the dose

received and the initial state of the subjects. The final outcomes of this study may thus change with time, and the results therefore require re-investigation with various factors considered to ensure complete justification. Nevertheless, when Interleukin-17-inihibitors were compared to other active drugs in previous studies, no increased risk of hypertension was observed in most cases. Madhur et al. (2010)examined the effects of the production of Interleukin-17 proteins on aorta to determine the resulting effects on vascular functions and hypertension, suggesting that Interleukin-17 can serve as a therapeutic for the treatment of hypertension. This implies that the suppression on Interleukin-17 by an antagonist may, in contrast, elevate blood pressure. In that study, the main focus was, however, on the effects of both Th-17 cells and Interleukin-17 on vascular dysfunction and hypertension.

Nguyen et al. (2013), however, examined the effects of Interleukin-17 on hypertension and suggested that increased levels of Interleukin-17-A were associated with hypertension. The mechanism of association between Interleukins and hypertension was unknown previously, and their study sought to understand the activity of Interleukin-17 on hypertension based on the hypothesis that endothelial nitric oxide might be responsible for this link. Their conclusion suggested that the activation of Interleukin-17 can indeed lead to hypertension, and they also thus suggested that inhibitors of Interleukin 17 (Ixekizumab, Secukinumab, and Brodalumab) can act as anti-hypertensive drugs in Interleukin associated inflammatory disorders.

In a study done by Amoruso et al. (2021), on the treatment of psoriasis, a popular antagonist of Interleukin-17, Ixekizumab, was investigated. The focus of that study was the effects of Interleukin-17 inhibition in terms of controlling the hypertension associated with renal dysfunction and psoriasis. They thus concluded that Ixekizumab can be safely used as drug of choice in the treatment of psoriasis as a way to control blood pressure levels. In another clinical study, (Gomez et al., 2017) suggested that Ixekizumab had no effect on blood pressure in healthy participants. That study focused on the response of various vaccinations in synergy with Ixekizumab in healthy subjects, as Ixekizumab is a common antagonist of Interleukin-17A, which can be used

to treat psoriasis. The results of the study suggested that there were no alterations in the levels of various vital signs, including systolic and diastolic blood pressure upon administration of Ixekizumab. In particular, the study indicated no effect from this antagonist on hypertension, and thus no risk associated with it in terms of increased blood pressure.

Pizzatti et al. (2020) assessed treatment of Erythrodermic Psoriasis with dialysis using Secukinumab. Erythrodermic Psoriasis is a condition associated with several additional complications, including hypertension, while due to the severe ADRs seen in various drugs in such cases, the majority of them are contraindicated.hypertension were increased due to the usage of other drugs in many cases, leading to renal failure; however, that research showed that the use of Secukinumab did not promote such complications, and it was concluded that there was no effect from Secukinumab in terms of blood pressure.

Smart et al. (2019) assessed the effects of two antagonists of Interleukin-17A on various cardiovascular outcomes including hypertension during psoriasis treatment. The antagonists chosen for that study were Brodalumab and Secukinumab. In patients with Interleukin-17A mediated disorders such as psoriasis, elevation of cardiovascular risks can occur. Due to the emergence of complications in several studies, a number of significant therapeutic approaches have thus needed to be discontinued. These biotherapies targeted the IL-17A receptors, but their more direct association with hypertension remains unclear. The mechanism behind such links thus requires further investigation in future, though that study indicated no alterations in the levels of blood pressure from any antagonists. Hence, where Brodalumab and Secukinumab are given in combination, no additional risk of hypertension is likely.

Most studies show no, or a very small, effect from Interleukin-17-inhibitors with respect to hypertension. Two studies indicated that Ixekizumab had no effect on hypertension, while two others suggested that Secukinumab decreased the risk of hypertension.A number of factors may influence or manipulate these outcomes, however. The first is whether the comparison made is between Interleukin-17-

inhibitors and other drugs: in most such cases, no significant increase of the risk of hypertension was seen. In the information collected for previous studies, no risk of hypertension has been associated with these drugs, though most have recommended further investigation, as the mechanisms behind the insignificant rise are unclear. Another possible cause of such outcomes may be that there was something common between certain subjects due to which the results were affected. Taking these factors in account, these effects need to be re-investigated and managed more carefully. However, most comparisons examined in the present study, and most of the previous studies, suggest that no increased risk of hypertension occurs when using Interleukin-17 inhibitors at standard doses.

6.5 Conclusion

It has been generally observed that these medications do not cause any significant risk of hypertension; however, as the mechanism of any small alterations is not clear, further investigations are needed. These biotherapies target IL-17A , making association with hypertension unclear, and the mechanism behind any possible link must thus be investigated in future studies. The basic effects of these inhibitors on hypertension were compared in this study and, In conjunction with various previous studies, it was concluded that there was no or only a very small effect of Interleukin-17-inhibitors on hypertension. All previous studies examined indicated that no significant risk of hypertension is associated with these drugs; nevertheless, most of these recommended further investigation on possible mechanisms. It can nevertheless be concluded that these Interleukin-17 inhibitors do not cause hypertension and that no significant increased risk of hypertension should be associated with these medications.

6.6 Strengths and Limitations

Various strengths and limitations of the study affected the outcomes either directly or indirectly. Before discussing the limitations of the study, it is thus important to highlight the strengths. Some cases did not justify the study's hypothesis completely, yet data and information that they provided was accurate and valid. Other data, collected from unpublished studies of trials by Lagley, Mclnnes, Huang, Braun, and Deodhar, were also included in this meta-analysis helping to improve the quality of some of the evidence. Along with these strengths, various limitations significantly influenced the research process and the final outcomes. The first limitation in the meta-analysis was the paucity of studies that supported the hypothesis. Very few studies provided any justification for the hypothesis, and, along with the rarity of any relevant results, a further limitation arose from the fact that the study justifications were not confirmed. Most investigators have mentioned that their results need further investigation, though none has mentioned the exact mechanism required for this. As such investigation is rare, the outcomes of this meta-analysis offer new and potentially beneficial information for future use, however. The second limitation of the study was that the outcome of interest, hypertension, is rare and while usually reported as an adverse event, is not designed to be detected as a primary outcome in any of the included trials. Further, no existing studies support the hypothesis independently. The sample size in most of the studies examined was thus small, except for those of Clarity and Future 5, who examined slightly larger groups, and an extensive sample size is required to allow more precise estimates of treatment effects.

These limitations, taken collectively, led to a lack of complete information in this study, while other limitations had less negative impact on the research. These included a lack of time and insufficient information in studies that required contact to be made with the authors to obtain more details. The data collection issues in the study led to some misinterpretation of results, however. Both the strengths and limitations of the study influenced the outcomes in positive and negative manners, respectively; however, overall, the outcomes are both logical and accurate.

7. Association between Interleukin 6 inhibitors and risk of hypertension

7.1 Introduction

Interleukin 6 (IL-6) is a protein that acts as a pro-inflammatory and an anti-inflammatory cytokine which is encoded by the IL6 gene in humans (Han et al., 2020). IL-6 protein is secreted by various cell types, such as T cells, B cells, monocytes, fibroblasts and osteoblasts (Fonseca et al., 2009).IL-6 plays a role in cell-mediated immune responses and the modulation of the immune system (Kaneko and Takeuchi, 2022) . IL-6 inhibitors act as therapeutic medication for various inflammatory diseases such as rheumatoid arthritis and neuromyelitis optica. IL-6 inhibitors have also been tested in the treatment of schizophrenia, depression, lymphoproliferative disorders, and cancer. Examples of IL-6 inhibitors include tocilizumab, elotuzumab, sarilumab, natalizumab, and vobarilizumab (Kang et al., 2019) . These drugs work by reducing chronic IL-6-mediated inflammatory signalling (Matthay and Luetkemeyer, 2021).

IL-6 inhibitors have significant side effects since they suppresses the immune system. IL-6 inhibitors may lead to infections, and consequently to severe complications since symptoms of any emerging infection are also suppressed. Anti- IL-6 medications also lead to neutropenia, elevations of hepatic enzyme and lipid elevation.IL-6 inhibitors also present certain risks in the development of cardiovascular events. For example, the use of tocilizumab in the treatment of rheumatoid arthritis poses a small risk for heart failure. Tocilizumab has warnings for gastrointestinal perforation and serious infections (Ridker and Rane, 2021). Sarilumab carries warnings for respiratory tract infections, neutropenia, hypercholesterolemia and gastrointestinal perforations (López et al., 2020).

7.1.1 Mechanism action of Interleukin-6 inhibitors

When IL-6 binds to its membrane-bound receptor, a glycoprotein 130 (gp130) transmits the signal to the cell membrane as indicated in **Figure 7-1 (A)**, in a process known as classical signalling (Zhang et al., 2017, Yu et al., 2022). In another type of

signalling, trans-signalling, IL-6 binds to the soluble IL-6 (sIL-6R) receptor forming a complex (IL-6/cIL-6R) which combines with gp130 for signal transmission. Trans-signalling through the sIL-6R can happen in any type of cell while classical signalling through membrane-bound receptors happens only in the haematopoietic system (Xiao et al., 2017) . It is easier for the IL-6/sIL-6R complex to bind to gp130 than for IL-6 to bind to its receptor, making it easier to block the latter.

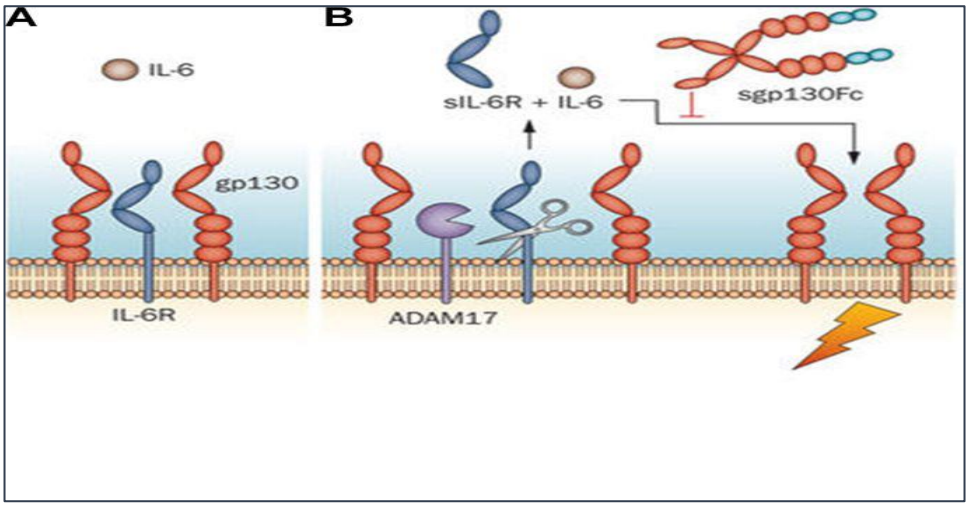

Figure 7-1 (A) depicts classical signalling between the IL-6 protein, IL-6 receptor (IL-6R0 and the gp130). **(B)** shows trans-signalling in which the soluble IL-6 receptor binds to Il- and the gp130 to transmit the signal indicated by the arrow.

Adapted from (Takeuchi et al., 2018a).

IL-6 inhibitors such as sarilumab and tocilizumab target the IL-6 receptor and inhibit both classical and trans-signalling. Other inhibitors such as olokizumab and clazakizumab target the IL-6 ligand. As illustrated in **Figure 7-2 (A)**, tocilizumab and sarilumab act on the second domain of the IL-6 receptor, thus preventing binding to IL-6 (Takeuchi et al., 2018a). These inhibitors do not interfere with binding to gp130 at the third domain. Monoclonal inhibitors such as clazakizumab prevent the IL-6 receptor from binding to IL-6 at site 1 **.** Olokizumab, another monocular inhibitor, prevents the fully functional receptor complex from interacting with gp130 at site 2 or site 3 **(**See **Figure 7-2 (B)).** Thus, different types of IL-6 inhibitors produce different blocking actions Those which act at site 1 result in higher increases in IL-6 systemic levels than those which bind at site 2 or 3.

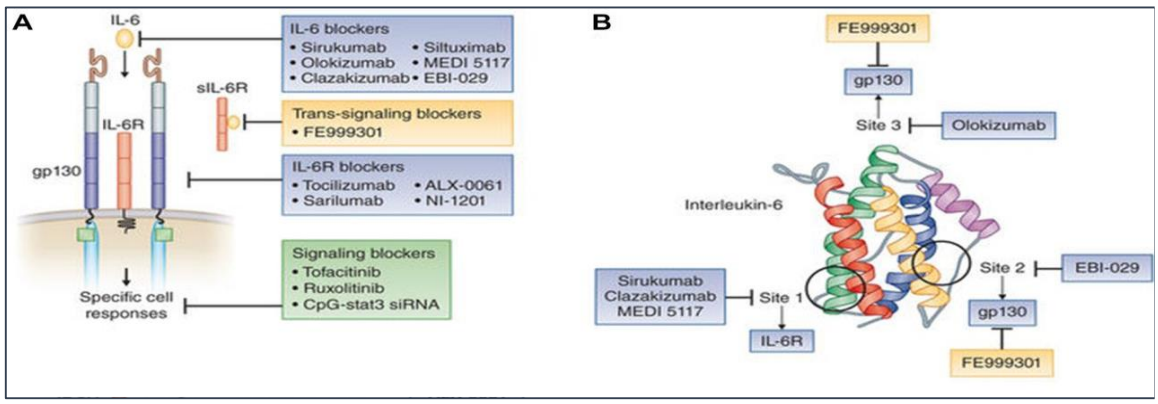

Figure 7-2 Different blocking actions of IL-6 inhibitors

Adapted from (Takeuchi et al., 2018a).

7.1.2 The hypothesis from basic science

Given the increasing prevalence of arterial hypertension, and the complex nature of pathogenesis mechanisms, medications which target inflammation as a means of antihypertensive therapy may be regarded as an innovative solution which merits further investigation. Evidence from laboratory testing shows that inhibiting IL-6 may control hypertension (Senchenkova et al., 2019) . However, though some monoclonal antibodies have been proven to reduce blood pressure in hypertensive patients, none have yet been approved to treat hypertension.

Laboratory tests conducted on mice show that the use of IL-6 inhibitors causes a reduction in blood pressure. Hashmat et al. (2015) conducted a research study with 14 lab rats. The researchers administered IL-6-neutralising antibodies and observed the mice's blood pressure over 11 days, to see whether this caused any change. The experimental group had significantly lower blood pressure compared to the control group. **Table 7-1** illustrates the various experimental findings which demonstrate the effects of interleukin 6 inhibitors.

Table 7-1 Selected previous pre-clinical studies.

Study	Design of study	Subjects	Follow-up period	Intervention	Summary of results
(Hashmat et al., 2016) Interleukin-6 inhibition attenuates hypertension and associated renal damage in Dahl salt-sensitive rats	Laboratory trial	14 Dahl salt-sensitive (SS) rats	11 days	Administering an IL-6 neutralising antibody to assess the role of IL-6 in the development of SS hypertension	IL-6 inhibition reduces hypertension in rats
(Lee et al., 2006) Angiotensin II hypertension is attenuated in interleukin-6 knockout mice	Laboratory trial	18 Mice	1 week	Administering IL-6 inhibitors in hypertensive mice under pressure and assessing their blood pressures.	IL-6 inhibition can potentially reduce blood pressure in hypertensive mice.
(Hashimoto-Kataoka et al., 2015) Interleukin-6/interleukin-21 signalling axis is critical in the pathogenesis of pulmonary arterial hypertension	Laboratory trial	22 mice	2 weeks	Administering IL-6 and Il-21 targeting agents	IL-6 inhibition prevents pulmonary hypertension in mice

7.1.3 Rationale for the current study

There is inadequate clinical research on the influence of IL-6 inhibitors on hypertension risk in human subjects. McInnes et al. (2015) conducted a randomised placebo-controlled study on 132 RA patients lasting 84 weeks. They concluded that IL-6 inhibitors regulate the concentration of lipids in the blood, increasing LDL and TG and thus modulate the risk of cardiovascular disease. Toshner et al. (2022) managed a randomisation study which involving the intravenous administering of tocilizumab, an IL-6 inhibitor, on 29 patients with group 1 pulmonary arterial hypertension. The results showed that tocilizumab had no benefit for patients suffering from pulmonary arterial hypertension. Finally, Provan et al. (2015) assessed the risk of developing cardiovascular disease in 24 patients taking tocilizumab and rituximab and noted a reduction in pulse wave velocity. However, there was no significant change in blood pressure. Thus, the impact of IL-6 inhibitors on the blood pressure of human patients remains unclear. Further clinical trials involving a variety of patients are necessary to accurately determine how IL-6 inhibitors affect blood pressure. Findings from the key randomised controlled trials which have been conducted are summarised in **Table 7-2**.

Table 7-2 Selected previous clinical studies

Title of study	Design of study	Subjects	Follow-up period	Intervention	Summary of results
(Toshner et al., 2022) Mendelian randomisation and experimental medicine approach to interleukin-6 as a drug target in pulmonary arterial hypertension	Randomised study	29 patients (10 male, 19 female with a mean age of 55 years) with group 1 Pulmonary arterial hypertension	6 months	Tocilizumab administered intravenously	The administration of tocilizumab did not affect patients with pulmonary arterial hypertension.
Elmedany et al. (2019) Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis	Randomised control trial	132 adult female RA patients.	24 weeks	Intravenous tocilizumab administered to the experimental group and Abatacept to the control group	Systolic blood pressure was significantly higher in the TCZ group.

7.2 Methodology

7.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

7.2.2 Data extraction

The initial search yielded 215 articles using the search strategies detailed in the Appendix A, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of those research articles reviewed (see **Figure 7-3**).

After removing duplicates, the remaining 170 citations or abstracts were assessed against inclusion criteria. Consequently, 122 articles were then eliminated based on a title and abstract review process, almost 50% of the total, as predefined by the PICOS framework. Of the 48 publications which remained eligible, thirty-one RCTs were further eliminated following a full-text screening process for a variety of reasons which are described in **chapter 3,Table 3-1**. Ultimately, seventeen trials comprising 11,835 patients formed the data set for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

7.2.3 Description of excluded studies

A total of thirty-one publications were excluded following an in-depth screening process of reading the full text. Three trials (Euctr, Heissgerova and Ikonomidis) reported different outcomes, which did not refer to hypertension (HTN). Three studies (Kurzrock, Rossi and Quartuccio) were excluded due to having a different research design, in this case being cohort studies. Four studies (Yokota,Aizawa,Woodman and Roswitch) were further excluded due to having different research designs, such as being cross-sectional or observational studies.

Six studies (Mollan, El Jammal, Dhilon, Rueda, Schirmer and Frampton) were not in fact trials, but reviews. Three studies were excluded because they had used Anti-Interleukin 6 in both arms (Wells, Ogata and Kume). Two studies (Kennedy and Van Rhee) which had a single arm design were also excluded.

The largest category of excluded studies was that of abstracts, conference proceedings, letters or reports of annual meetings which had incomplete results. in **chapter 3,Table 3-1** summarises the reasons for elimination for each piece.

7.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.
Sensitivity analyses were conducted to understand the impact of excluding studies with [1] weak methodologies and a high risk of bias (RoB); [2] small sample sizes (less than 100 l participants).

Subgroup analyses for Anti-IL6 studies were performed as follows: [1] comparator drugs; [2] clinical setting; [3] duration of follow-up.

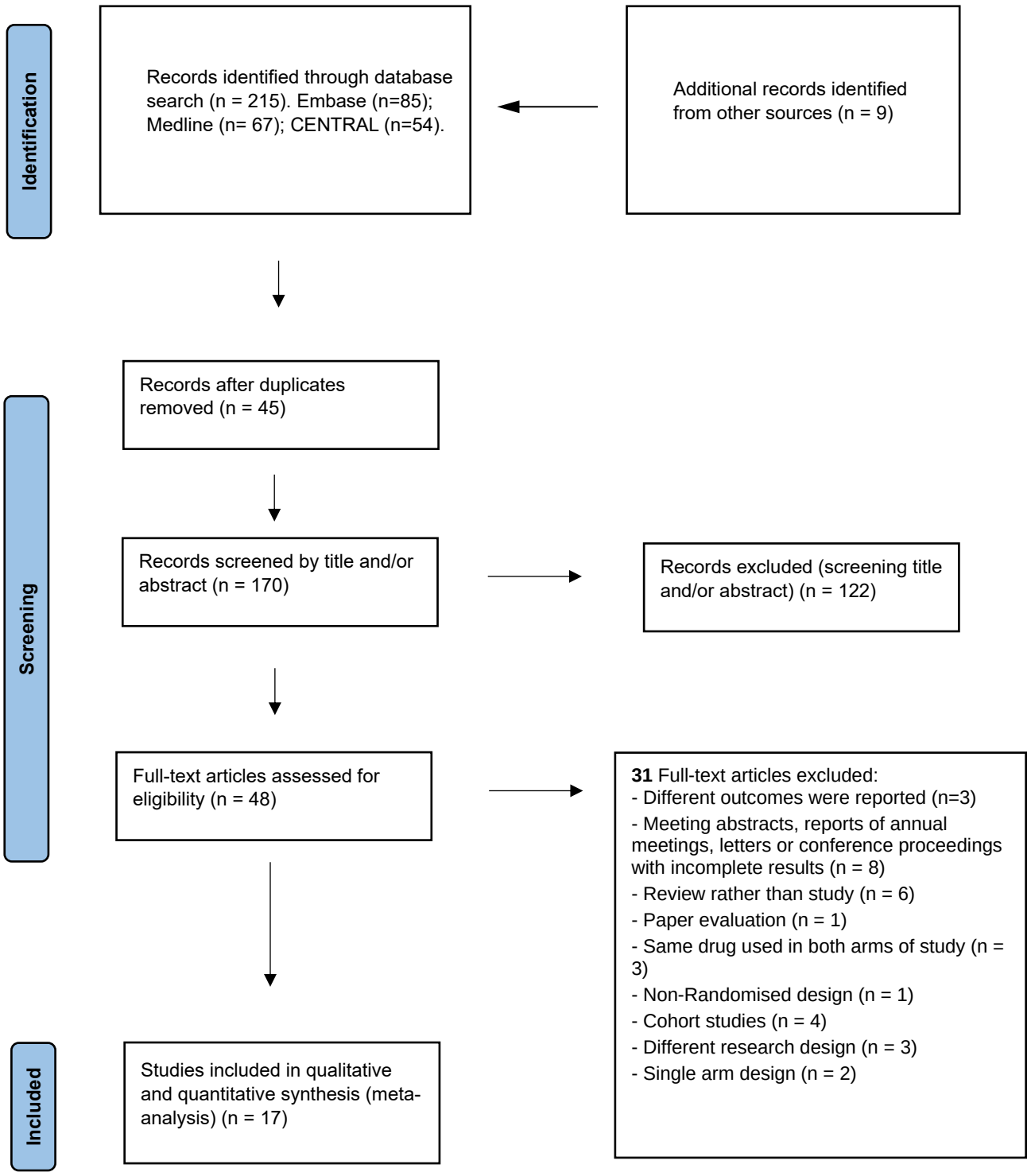

Figure 7-3 PRISMA Study flow diagram

7.3 Results

In total, there were seventeen eligible Anti-IL6 trials. These studies incorporate 11,835 patients, with an average follow-up period of 1.25 years (ranging from five months to five years).

The average patient age across all trials was fifty years old.

Figure 7-3 provides a summary of the trial searching and identification process.

Thirty-one studies were excluded for logical reasons. **Table 3-1 in chapter 3** records the reasons for each study's exclusion. Seventeen RCTs (randomized controlled trials) formed the data for the final review.

The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

All of the included studies were published after the year 2000. However, the most recent studies which were included were published in 2020 (Nasonov and Giles).

Two studies were published in 2008 (Option and Toward). Both of these studies used Tocilizumab compared to a placebo in the treatment of rheumatoid arthritis; however, the Toward study featured two arms combined with conventional disease modifying antirheumatic drugs (DMARDs). Three studies published in 2016 (Fasscinate, Bijlsma and Monarch) used Tocilizumab, except for the Monarch study, in which they used different anti-IL6 agents (Sarilumab).

The Sirround-T and Sirround-H studies were both phase three clinical trials using Sirukumab in patients with active rheumatoid arthritis. However, they used different comparators: h Sirround-T compared to a placebo and Sirround-H compared to Adaliumab. Both studies reported several patients experiencing adverse effects, one of which was hypertension.

Ten studies compared Anti-IL6 with a placebo (Burmester, Fasscinate, Kakehasi, Lithe, Nasonov, Rhee, Rose, Sirroind-T, Option and Toward) with all of them reporting hypertension as an adverse event.

Seven studies compared Anti-IL6 to active controls involving Methotrexate, or other anti-TNF agents, and these were divided into subgroups for the purpose of analysis (see **Figure 7-8**).

In Rose's study all patients had a background of disease-modifying antirheumatic drugs (DMARDs) in both groups and the Toward study further combined DMARDs in both groups. In the Option study, they compared a placebo with different doses of Tocilizumab (8 mg and 4 mg per kg) in two different groups. The Lithe study also used different doses of Tocilizumab (8 mg and 4 mg per kg) compared to a placebo in patients with rheumatoid arthritis.

Most studies employed a double-blind design except for two (Giles and Visara) which used an open-label design. However, the Lithe study used both double-blind and open-label designs in three groups: in the first year they used double-blind design in all groups; at the end of year one, two groups still used double-blind design except one group that used Tocilizumab 8 mg/kg, which switched to an open-label design until the end of year two. All groups in the study were extended for three years (so the study lasted five years in total), with all of them employing an open-label design from this point onwards.

The follow-up study periods ranged from five months to five years. All the study participants were adults with a mean age of fifty years old. There were no single-sex studies but the proportion of male and female participants differed from study to study.

Anti-interleukin 6 agents now covers a range of drug treatments and different studies used different drugs such as Tocilizumab, Sarilumab, Sirukumab, Siltuximab, Olokizumab, Elsilimomab, Clazakizumab and Levilimab (all of which medications were keyword search terms). The most commonly used drug was tocilizumab, which was used in Burmester, Fasscinate, Lithe, Rose, Option, Toward, Adacta, Ambition, Bijlsms, Giles and Visara. Kakahasi and Monarch used Sarilumab, while the Sirroind-T and Sirroind-H studies used Sirukumab. Situximab was used in the Rhee study, and Olokizumab was used in the Nasonov study.

Most studies involved participants who had been diagnosed with rheumatoid arthritis, except for the Fasscinate report, in which patients were diagnosed with systemic sclerosis, and the Rhee study in which patients were diagnosed with Castleman disease. Details of participants background conditions are given in **Table 7-3.**

Table 7-3 The underlying disease of each trial

Trial	Background condition	Trial	Background condition
Burmester 2016	rheumatoid arthritis	Toward 2008	rheumatoid arthritis
Fasscinate 2016	systemic sclerosis	Adacta 2013	rheumatoid arthritis
Kakehasi 2019	rheumatoid arthritis	Ambitoin 2009	rheumatoid arthritis
Lithe 2013	rheumatoid arthritis	Bijlsma 2016	rheumatoid arthritis
Nasonov 2020	rheumatoid arthritis	Giles 2020	rheumatoid arthritis
Rhee 2014	Castleman disease.	Manarch 2016	rheumatoid arthritis
Rose 2012	rheumatoid arthritis	Sirround-H 2017	rheumatoid arthritis
Sirroind-T 2017	rheumatoid arthritis	Visara 2013	rheumatoid arthritis
Option 2008	rheumatoid arthritis		

Ten studies directly compared Anti-IL6 with a placebo, incorporating the data from 6,523 patients. Anti-IL6 was compared to other active drugs in seven studies, incorporating data from 5,312 patients. The pooled estimate from the random-effects meta-analysis showed no statistically significant difference in the risk of hypertension between Anti-IL6 and a placebo (RR = 1.2, 95% CI 0.82; 1.73, P = 0.35). A total of 93 (2.1%) and 37 (1.7%) events occurred in the Anti-IL6 and placebo groups, respectively. No heterogeneity was observed between studies (I2 = 0%, P = 0.89). Three studies were assigned approximately three-quarters of the meta-analysis weight; these were Sirroind-T, Option, and Toward. The effect size was not statistically significant in the studies.

When Anti-IL6 was compared to other active drugs, no statistically significant difference was observed in the risk of hypertension between groups (RR = 1.48, 95% CI 0.97; 2.25, P = 0.07), although the results suggested a slightly higher risk of hypertension in patients who received Anti-IL6. A total of 78 (2.8%) and 37 (1.5%) events occurred in the Anti-IL6 and active drug groups, respectively. The effect size was statistically significant in only one study. Sirroind-H which was assigned one-quarter of the meta-analysis weight (27.4%). Low heterogeneity was observed between studies (I^2 = 7%, P = 0.37) (See **Figure 7-4**).

Similar results were obtained when fixed-effects model was used (**Figure 7-5**). The difference in risk of hypertension was not significantly significant between Anti-IL6and the placebo groups (RR = 1.24; 95% CI 0.86; 1.78, P = 0.25). Four of the ten studies contributed to 90% of the meta-analysis weight (studies Kakehasi, Sirrond-T, Option, and Toward). The risk of hypertension was significantly higher in Anti-IL6 than other active drugs and the pooled estimate was statistically significant (RR = 1.53, 95% CI 1.04; 2.24, P = 0.03).

The assessment of the funnel plot shown in **Appendix D, Figure D-4** demonstrates a reasonably symmetrical distribution of studies on either side of the plot. No outlier studies can be detected. These characteristics suggest that the meta-analysis has no publication bias.

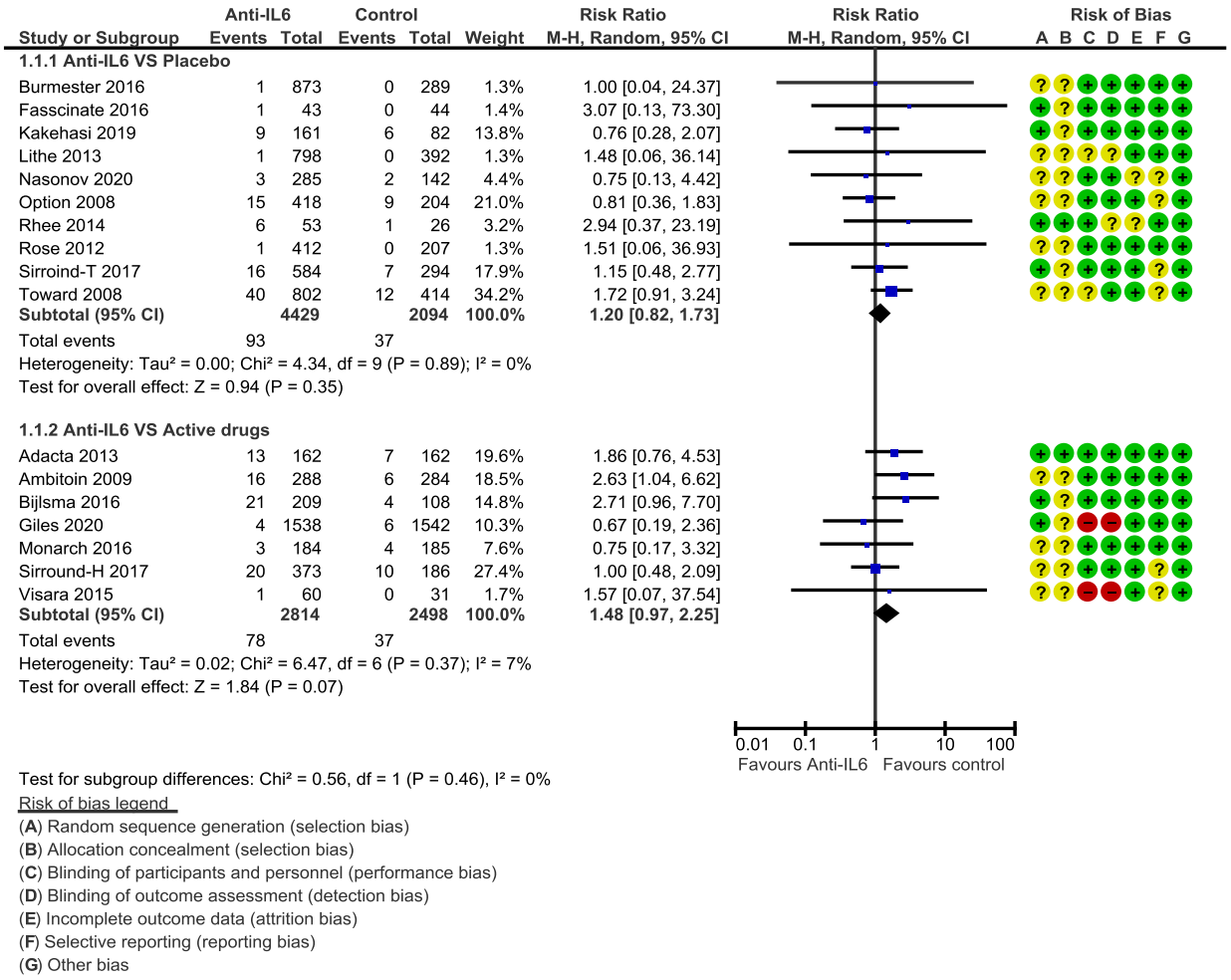

Figure 7-4 Random-effects model for the association between Anti-IL6 and the risk of hypertension

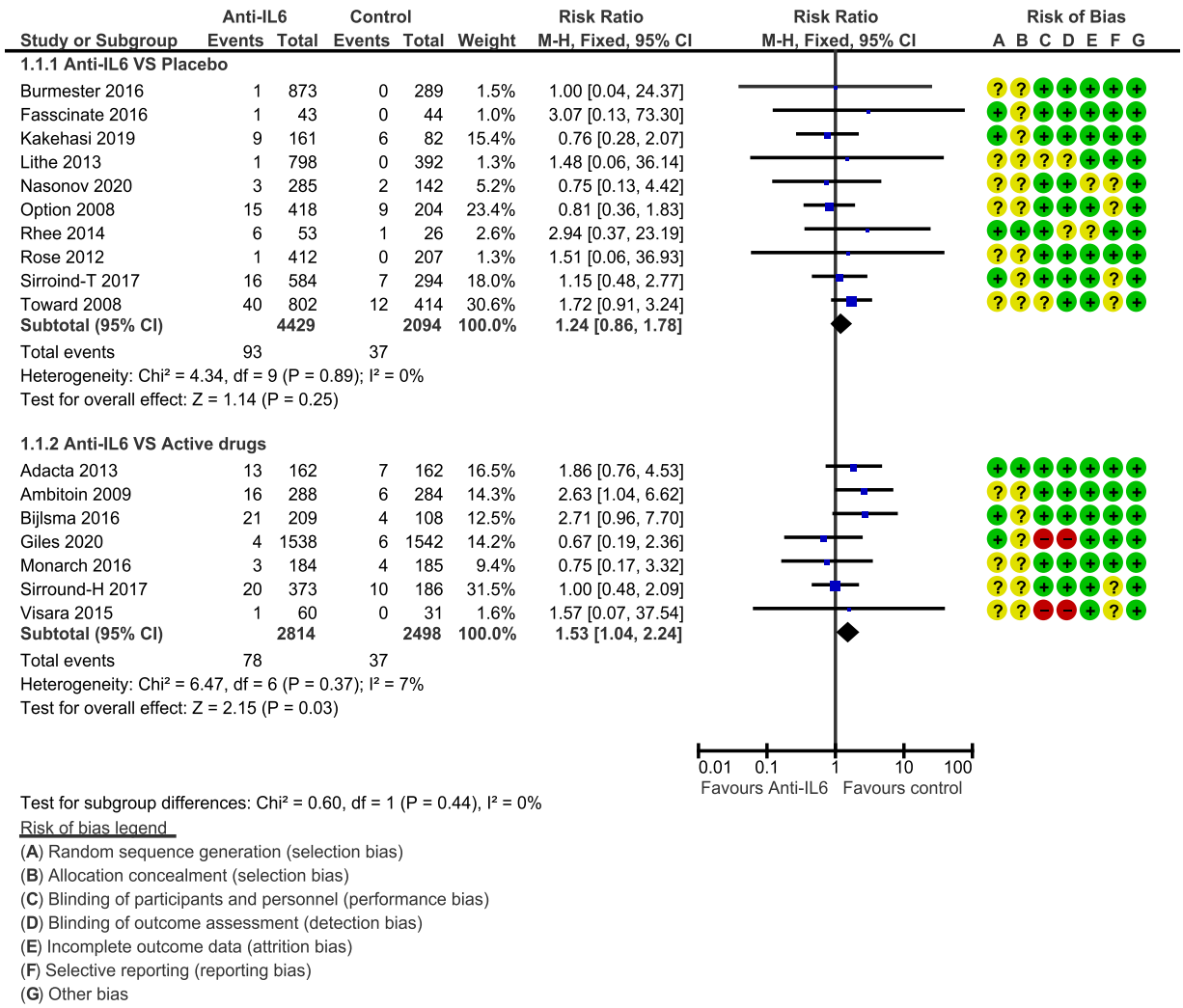

Figure 7-5 Fixed effects model for the association between Anti-IL6 and the risk of hypertension.

7.3.1 Sensitivity analyses

Sensitivity analysis was performed to assess the robustness of estimates. The association between the use of interlukine-IL6 and the incidence of hypertension was evaluated after excluding (1) studies with a high risk of bias due to weak methodology; (2) studies with a small sample size (of under 100 participants).

As **Figure 7-6** shows, five studies were included in the active drugs subgroup after the exclusion of two studies (Giles and Visare) which had a high risk of bias. A statistically significant association was observed between the use of Anti-IL6 and the risk of hypertension (RR = 1.63, 95% CI 1.02; 2.6, P = 0.04). A total of 73 and 31 events occurred in Anti-IL6 and the active drugs groups, respectively. Low heterogeneity was observed between studies (I^2 = 16%, P = 0.31).

Three studies with small sample sizes were excluded from the analysis. In the placebo subgroup, two trials were excluded (Fasscinate and Rhee). In the active drugs subgroup, one trial was excluded (Visara). Eight studies directly compared Anti-IL6 to a placebo, incorporating 4,333 and 2,024 patients, respectively. Anti-IL6 was compared to other active drugs in six studies incorporating 2,754 and 2,467 patients, respectively. The pooled estimate from the RE meta-analysis showed that there was no statistically significant difference in the risk of hypertension between Anti-IL6 and the placebo (RR = 1.14, 95% CI 0.78; 1.67, P = 0.49). A total of 86 and 36 events occurred in Anti-IL6 and the placebo groups, respectively. No heterogeneity was observed between studies (I^2 = 0%, P = 0.87). When Anti-IL6 was compared to other active drugs (after excluding studies with small sample sizes), no statistically significant difference was observed in the risk of hypertension between groups (RR = 1.48, 95% CI 0.93; 2.35, P = 0.1), although the results suggested higher risk of hypertension in patients who received Anti-IL6. A total of 77 and 37 events occurred in Anti-IL6 and the active drug groups, respectively. Low heterogeneity was observed between studies (I^2 = 23%, P = 0.26) (see **Figure 7-7**).

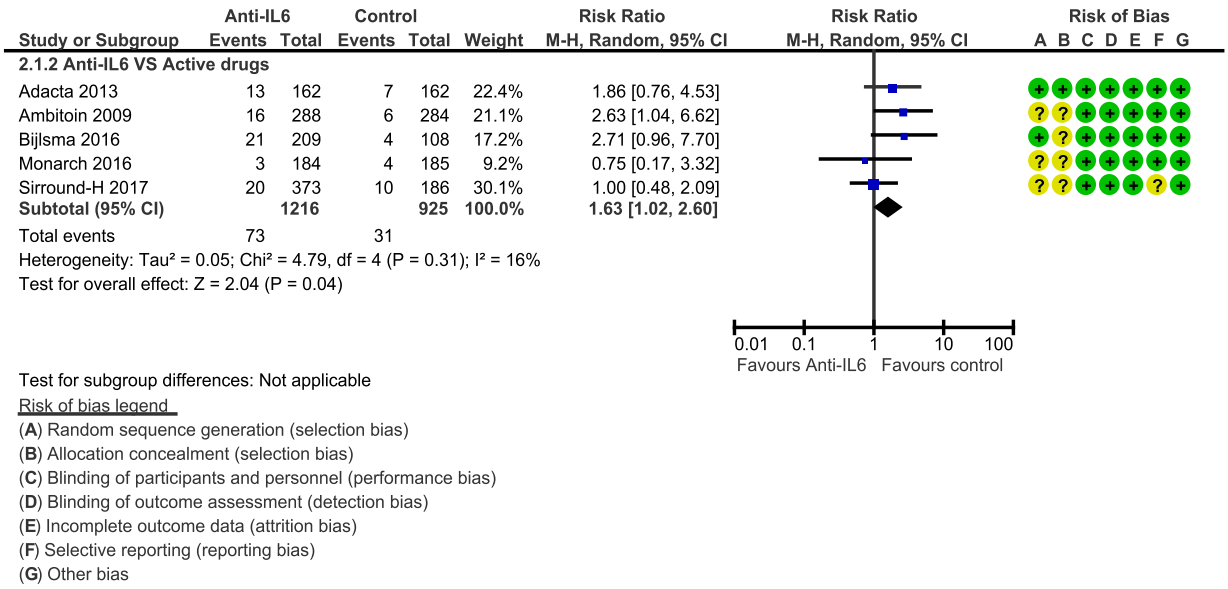

Figure 7-6 Sensitivity analysis for the association between Anti-IL6 and the risk of hypertension. (Studies with high risk of bias were excluded).

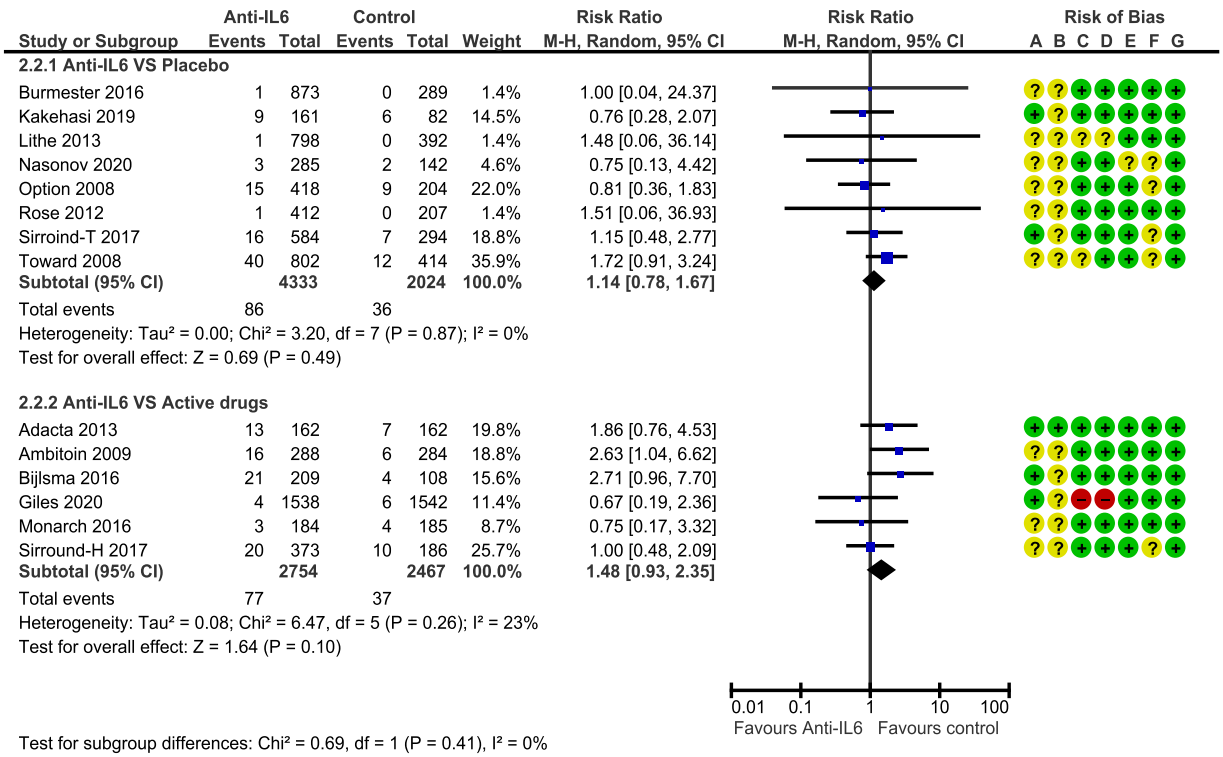

Figure 7-7 Sensitivity analysis for the association between Anti-IL6 and the risk of hypertension. **(**Studies with low sample size (< 100) were excluded).

7.3.2 Subgroup analyses

Table 7-4 summarises the subgroup analyses of Anti-IL6s' impact on hypertension risk. The analysis, which included active drugs, was stratified by the type of comparator into two different subgroup analyses. Three studies compared Anti-IL6 to methotrexate, and four to Anti-TNFs. For the subgroup analysis involving Anti-TNF drugs, no association was observed between Anti-IL6 and the risk of hypertension (RR = 1.1, 95% CI 0.67; 1.79, P = 0.71). No heterogeneity was observed between studies (I^2 = 0, P = 0.52). When Anti-IL6 was compared to methotrexate, the risk of hypertension was significantly higher in Anti-IL6 (RR = 2.6, 95% CI 1.32; 5.12, P = 0.006). No heterogeneity was observed between studies (I^2 = 0, P = 0.95) (see **Figure 7-8**).

Only two studies included patients with HTN at baseline (see **Figure 7-9**), which had opposite effect sizes, although neither of them was statistically significant. The pooled estimate from the RE model was not statistically significant (RR = 0.75, 95% CI 0.23; 2.42, P = 0.63). The remaining 15 studies included patients with no HTN at baseline. The pooled estimate revealed a significantly higher risk of hypertension in patients who received anti-IL6 than those who received active comparators (RR = 1.36, 95% CI 1.03; 1.8, P = 0.03). No heterogeneity was observed between studies (I^2 = 0%). Several factors could account for the effect on blood pressure observed in patients who are not hypertensive at baseline, but not evident in patients with pre-existing hypertension. One possibility is that the number of drugs taken at baseline might affect a patient's response to hypertension medication; those patients who take a greater number of medications might respond better to treatment. Another possible factor is that the generalisability of a study is influenced by the demographics of the population. As Crowley et al. (2016) point out, there are often differences between BP measurements obtained in research and clinicall settings; the measurements obtained in research more often categorise patients "in control".

Five studies included patients who were followed up for two years or more and twelve included patients who were followed up for less than two years. Both subgroup analyses did not reveal an association between the use of Anti-IL6 and the risk of a hypertension (RR = 1.31, 95% CI 0.98; 1.76, P = 0.07) and (RR = 1.37, 95% CI 0.68; 2.75, P = 0.37) . No heterogeneity was observed between studies in both subgroups (I^2 = 0%). These results indicate that the duration of follow-up does not affect the observed effect of Anti-IL6 on the risk of hypertension (see **Figure 7-10**).

Table 7-4 Summary of a meta-analytical subgroup analysis by RE model demonstrating the effect of interlukine-6 inhibitors compared with controls (placebo and active) on the risk of hypertension

Subgroup analysis		Studies		Participants	Events	Hypertension Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%)
						Anti-6	Control			
Overall	RE	Placebo	10	6523	130	2.09	1.7	1.20 [0.82,1.73]	0.35	0
		Active drugs	7	5312	115	2.7	1.4	1.48 [0.97,2.25]	0.07	7
Type of comparator	Methotrexate		3	980	48	6.8	2.3	2.60 [1.32,5.12]	0.006*	0
	Anti-TNF		4	4332	67	1.7	1.3	1.10 [0.67,1.79]	0.71	0
Clinical setting	Hypertension at baseline**		2	3699	11	0.25	0.34	0.75 [0.23,2.42]	0.63	0
	No hypertension at baseline**		15	8136	234	3.1	2.4	1.36 [1.03,1.80]	0.03	0
Duration of follow-up	Less than two years**		12	6202	203	3.5	2.8	1.31 [0.98,1.76]	0.07	0
	Two years or Longer**		5	5633	42	0.92	0.50	1.37 [0.68,2.75]	0.37	0

† **list of definitions and abbreviations**: CI: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant.; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity.;** Placebo and active drugs have been combined.

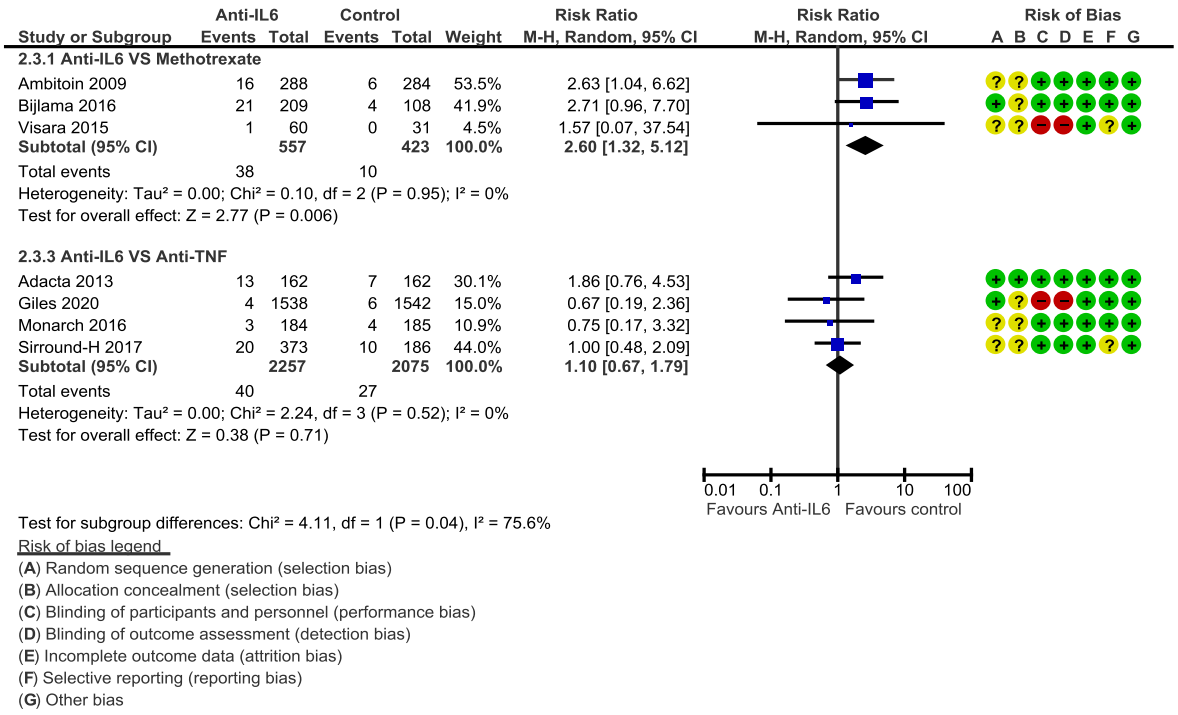

Figure 7-8 Subgroup analysis for the association between Anti-IL6 and the risk of hypertension. (The analysis was stratified by the type of comparator).

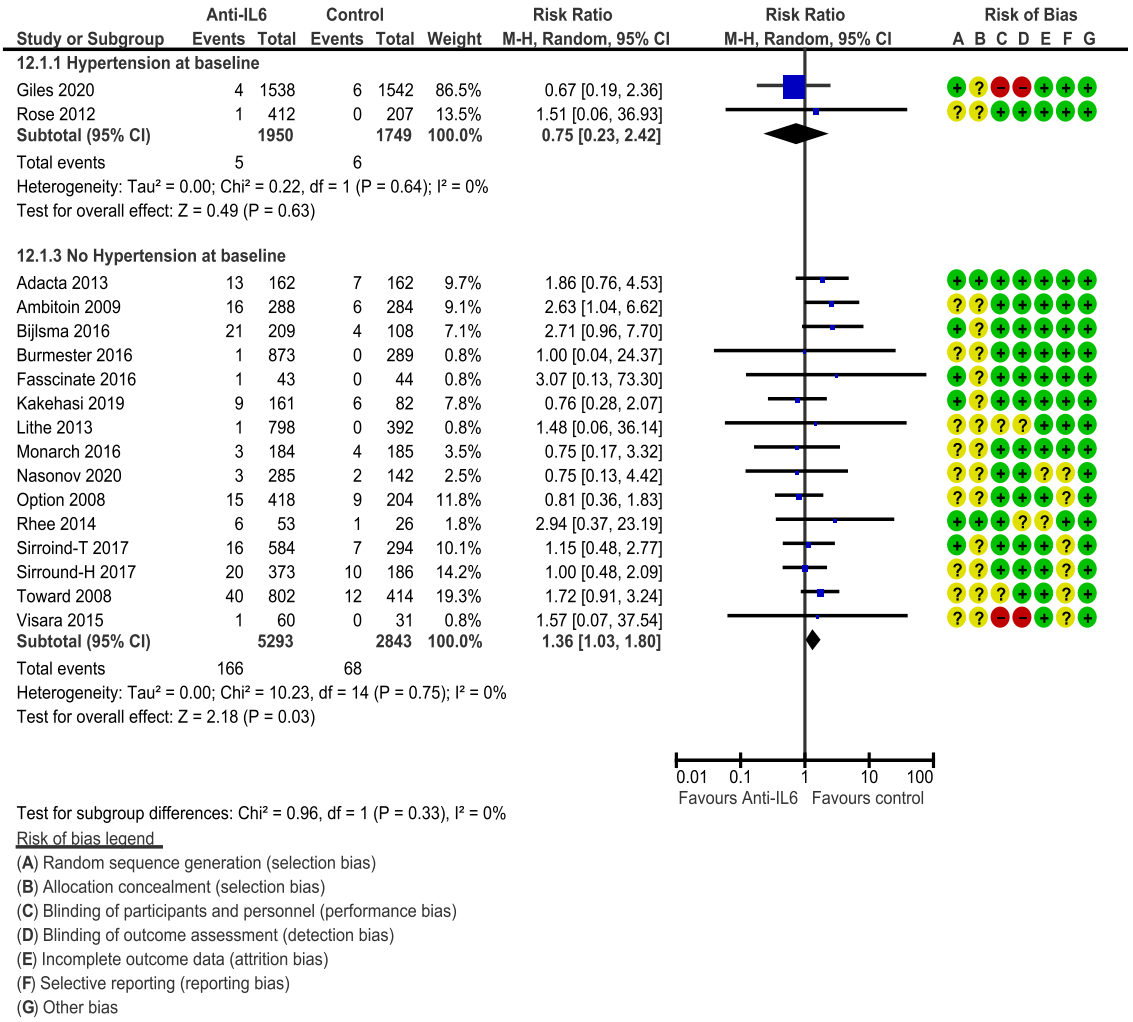

Figure 7-9 Subgroup analysis for the association between Anti-IL6 and the risk of hypertension. (The analysis was stratified by clinical population setting. Placebo and active groups were combined).

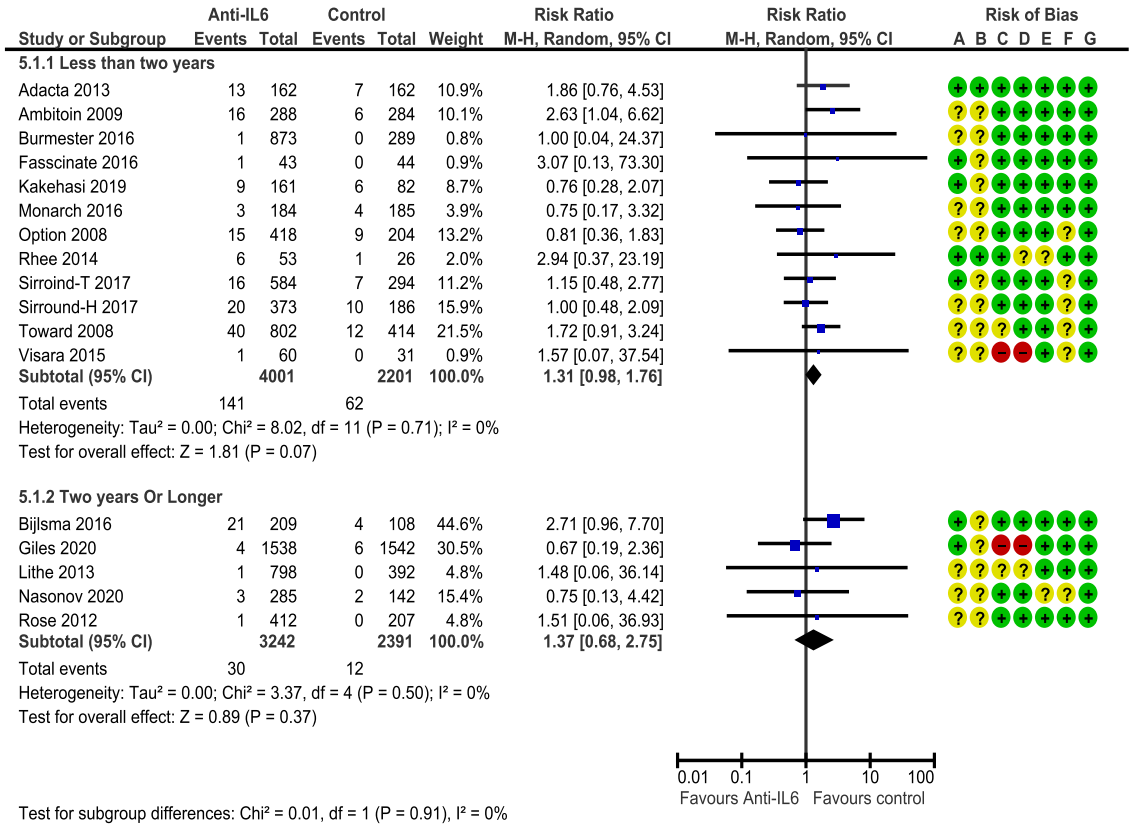

Figure 7-10 Subgroup analysis for the association between Anti-IL6 and the risk of hypertension. (The analysis was stratified by the duration of follow-up. Placebo and active groups were combined).

7.4 Discussion

The outcomes from this study indicate that the meta-analysis of the hypothesis that Interleukin-6 inhibitors do not cause a risk of hypertension. Interleukin-6 plays a significant role in various physiological abnormalities. Sarilumab and Tocilizumab are the most commonly used Interleukin-6-Inhibitors (Yip and Yim, 2021). However, some suggest that the risk of hypertension increases due to these drugs only in a very small proportion, while other evidence suggests that attenuation occurs in the blood pressure due to the use of these medications. Interleukin-6 is one of the pleiotropic cytokines. These cytokines promote various types of immune responses like inflammation (Tournadre et al., 2017). The findings of this research show that Interleukin-6-inhibitors, when compared to placebo and active drugs, significantly showed no risk of hypertension. Interleukin-6 inhibitors are mainly used to treat various diseases like rheumatic diseases, various types of cancers, and COVID-19 (Nasonov and Samsonov, 2020). The present study finds no hypertension-associated risk with these drugs.

In the present review study of the effect of Interleukin-6 inhibitors on blood pressure, it has been suggested that these medications do not cause a risk of hypertension. Interleukin-6 inhibitors were compared to a placebo and active drugs such as anti-TNF drugs, and methotrexate. In the comparison of Interleukin-6 inhibitors with a placebo, the pooled estimate did not show a substantial difference in the risk of hypertension; the results of this comparison were (RR = 1.2, 95%, CI = 0.82; 1.73, P = 0.35). The number of events that occurred in Interleukin-6 inhibitors was 93 (2.1%) and with the placebo there were 37 (1.7%) events.

In another comparison of Interleukin-6 inhibitors with active drugs, no substantial difference was detected with regards the risk of hypertension. The results of this comparison were (RR = 1.48, 95% CI 0.97; 2.25, P = 0.07). Similarly, this comparison did not exhibit a risk of hypertension. In the case of sensitivity analysis, there were five studies related to active drugs, and two studies were excluded due to risk of bias (RoB). As a result, it was observed that interleukin-6 inhibitors show a statistically noteworthy association with the risk of hypertension. The overall

outcomes of this were (RR = 1.63, 95% CI 1.02; 2.6, P = 0.04). The active drugs were classified into two subgroups depending upon the type of comparator. The active drugs were compared to Anti-TNFs and Methotrexate, respectively. In the first analysis of Interleukin-6inhibitors with Anti-TNF drugs, no association was observed with the risk of hypertension. When compared to Methotrexate, the risk of hypertension was higher in Interleukin-6 inhibitors. The results of these outcomes were (RR = 1.1, 95% CI 0.67; 1.79, P = 0.71) and (RR = 2.6, 95% CI 1.32; 5.12, P = 0.006), respectively. In the comparison of Interleukin-6 inhibitors with Anti-TNFs no risk of hypertension was observed in either, but when compared with methotrexate, Interleukin-6 inhibitors showed some risks of hypertension.

In another study, the population was divided into subgroups. The first group consisted of individuals with hypertension, while the second group consisted of those without hypertension. In the first group, those with hypertension at baseline, the pooled estimate was not statistically significant, while in those with no hypertension the pooled estimate showed surprisingly that there was a significantly high risk in those who received Interleukin-6 inhibitors than those who received comparators only. The results of this comparison were (RR = 0.75, 95% CI 0.23; 2.42, P = 0.63) and (RR = 1.36, 95% CI 1.03; 1.8, P = 0.03), respectively. Overall, findings suggest that there is no significant effect of Interleukin-6 inhibitors on the risk of hypertension associated with the use of these medications.

However, while a number of previous studies support the results presented here, the results of these studies can vary depending upon the dose, the type of study, and the individual participant’s state. Additionally, the outcomes of the present study can wane with time. The present study suggests that when the Interleukin-6 inhibitors were compared to a placebo and some active drugs, there was no difference in results. When the same drugs (Interleukin-6 inhibitors) were compared to Anti-TNFs, no risk of hypertension was observed but in the case of Methotrexate, the hypertension risk was greater in the Interleukin-6 inhibitors group.

A study done by Anne and Bruno suggests that when Interleukin-6 inhibitors are used against Rheumatoid Arthritis, and the body composition and the metabolic profiles of participants are evaluated, there is no change in blood pressure,in this study, the main focus was on the alteration in the levels of metabolic profile and various body fluid compositions (Tournadre et al., 2017). The antagonists of Interleukin-6 cause a reduction in the inflammation in various inflammatory disorders, but the concentration of certain lipids increases in some cases. In a study by Iain and Thompson, where Interleukin-6 inhibitors were tested for vascular risk in both Interleukin-6 inhibitor and placebo groups, there was no evidence of blood pressure alteration (McInnes et al., 2015) . In another similar study, Norihiro and Kazuyuki found that there was an increase in blood pressure but they also mentioned that this finding needed further research (Nishimoto et al., 2004) . According to all the above-mentioned studies it can be suggested that Interleukin-6 inhibitors do not affect blood pressure. However, in the latter study surprisingly there was an unexpected increase in the level of blood pressure but there was no strong explanation for this finding.

A previous study by Genovese and McKay examined Interleukin-6 inhibitors for their effectiveness and safety assessment of antibodies combined with some other drugs in an individual with Rheumatoid Arthritis. As a result, it was proved that the antagonists of Interlukin-6 used to treat Arthritis found an increase in hypertension as a comorbid condition in the control group, but this increase was only found in a very small proportion of participants (Genovese et al., 2008).

Hypertension is one of the most common causes of deaths worldwide. Other diseases commonly associated with hypertension include cardiovascular disease, which can also lead to renal disease. There are several studies which indicate that alteration in the levels of cytokines can be directly or indirectly responsible for hypertension. The Interleukin-6 antagonists bind to the receptors and inhibit proinflammatory properties. These drugs correlate with various types of diseases by suppressing the activity of Interleukins-6. Tocilizumab is an antibody that is a novel method that can be used in several treatments. In another study by Shireen and Nathan, the inhibition of Interleukin-6 was shown to reduce hypertension. This study demonstrated that Interleukin-6 is a type of proinflammatory cytokine and

that their inhibition can cause a reduction in blood pressure through a number of mechanisms. Therefore, only a single mechanism cannot be considered conclusive (Hashmat et al., 2016).

Thus, there is either no or very small effect of Interleukin-6 inhibitors on hypertension. The results presented in this study are in agreement with previous studies on the relationship between Interleukin-6 inhibitors and the risk of hypertension (Burmester et al., 2017a, Fleischmann et al., 2013) . There are several factors which contribute to this outcome. Firstly, all of the comparisons made between Interleukin-6 inhibitors and other drugs showed no difference, and no risk of hypertension was associated. When compared to methotrexate, a minor risk of hypertension was observed in Interleukin-6 inhibitors. The risk in the case of a comparison between Methotrexate and Interleukin-6 inhibitors was mainly due to the AMBITION study, which constitutes more than half of the full weight. In the AMBITION study, the methotrexate group had a higher number of patient discontinuations (Jones et al., 2010). Therefore, the present study needs repeating to help justify and prove this result. Secondly, according to a previous study, an increased risk of hypertension was indicated thus these two studies can be an indication that there may be some factors that can cause an increased risk of hypertension. There may be something common to these two patient populations causing these similar results which need to be investigated and controlled for. However, most of the comparisons in the present study along with most of the previous studies suggest and indicate that no risk of hypertension by using Interleukin-6 inhibitors at standard doses.

7.5 Strength and limitations

This research includes all publicly available information reported to date and is the largest meta-analysis of RCTs studying the relationship between anti-IL6 and the risk of hypertension.

Furthermore, unpublished hypertension data from the Burmester, Monarch, Bijlsma, Lithe, Nasonov, Rose, Giles and Visare trials were included in this meta-analysis, improving the quality of the evidence by drawing on all available sources.

The reliability of the results across several sensitivity analyses assists the robustness of the primary results. Additionally, the pooling of results from all the included trials was supported by the almost complete disappearance of statistical heterogeneity. Nevertheless, there are important limitations to this analysis. Hypertension, which is usually reported as an adverse event, was not designed to be detected as a primary outcome in any of the included trials. Most studies had small sample sizes except Giles, which was slightly larger, but an extensive sample size is required to allow a more precise estimate of the treatment effect and also decreases the possibility of having accidentally extreme or biased groupings. All RCTs have a short average follow-up period of five months to five years. Therefore, this meta-analysis reports the risk of bias because some studies have unclear allocation sequences described without further details, insufficient detailing of concealment schemes or stratification, and incomplete information and also in random sequence generation. Furthermore, the methodology used was described in insufficient detail in some trials.

There remains the possibility that unpublished studies might have been missed despite a thorough, comprehensive search of databases and clinical trial registers. The effect of Interleukin-IL 6 inhibitors on hypertension has not been the subject of enough research and more studies on this particular topic are needed to improve knowledge in this field.

7.6 Conclusion

In total, data from 11,835 patients was included in this meta-analysis of RCTs. Years of follow-up have shown that interleukin-6 inhibitors pose no risk of hypertension in patients with autoimmune diseases. While an insignificant risk of hypertension was found when methotrexate was compared to interleukin-6 inhibitors, this may be due to other reasons relating to those particular studies using methotrexate. Like most previous studies, the results of this research demonstrate no risk of hypertension from IL-6 inhibitors, but more evidence is needed to render this conclusion definitive.

8. Association between Purine and Pyrimidine inhibitors and risk of hypertension

8.1 Introduction

Purine inhibitors are a class of drugs that work by inhibiting the formation of purines, which are important building blocks for DNA and RNA. By blocking the production of purines, these drugs can inhibit the growth and replication of cells (Pedley and Benkovic, 2017).The inhibitors of Pyrimidine have been used to treat a variety of conditions, including cancer, autoimmune diseases, and transplant rejection. They are particularly effective in treating certain types of blood cancers such as leukemia because they target rapidly dividing cells (Russell, 2017).
Similarly, pyrimidine inhibitors are a class of drugs that work by inhibiting the formation of pyrimidines, which are also important building blocks for DNA and RNA. By blocking the production of pyrimidines, these drugs can likewise inhibit the growth and replication of the cells (Schenone et al., 2014).

The safety concerns for Azathioprine can be considered more carefully through various clinical experiences of this medication. Azathioprine is used for various types of treatments, including Inflammatory bowel disease, Organ Transplantation, and Rheumatoid Arthritis. The subsequent side effects found in these clinical experiences were Bone Marrow Depression, Fever, Pancreatitis, and Nausea (Connell et al., 1993). In several clinical practices Azathioprine has shown to be less effective due to low-dosing and toxicity concerns (Ginzler et al., 1975).

The FDA approved Azathioprine in the 1968s with the intention of treating patients with Kidney Transplant (Mahida et al., 2018).Therefore, over the past fifty years, the medication has had limited uses, reserved for the treatment of several disorders like Hematologic Malignancies, Inflammatory bowel disease, Rheumatologic Disorders, and various Organ Transplants. During its testing phase in 1958, this medication revealed antigen-specific tolerance in rabbits. In this experiment, unfortunately, the tolerising effects of Azathioprine became less robust in cases of Organ Transplants, which results in the movement toward new

and more potent immunosuppressive drugs, anti-proliferative drugs, and Mycophenolate Mofetil (Maltzman and Koretzky, 2003).

The medication was approved by the FDA to be used for the prevention of various medical conditions, including Renal Homo-transplantation Rejection. Many Chronic, intermittently progressive, and fatal autoimmune diseases can be treated by using the medication, including regional enteritis, ulcerative colitis, chronic active hepatitis, biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematous, glomerulonephritis, the nephrotic syndrome, hematologic diseases, skin diseases, multiple sclerosis, asthma, and several other disorders (Rosman and Bertino, 1973).

Azathioprine can cause a range of side effects, varying in severity and frequency. Some of the most common side effects include nausea, vomiting and abdominal pain (Kissel et al., 1986).

Leflunomide is a disease-modifying, anti-rheumatic drug (DMARD), meaning that it can slow down the progression of the disease and reduce damage to joints and other tissues. Leflunomide works by inhibiting the enzyme Dihydroorotate Dehydrogenase (DHODH), which is involved in the de novo pyrimidine synthesis. Leflunomide was first developed by Sanofi-Aventis (Papadopoulou et al., 2012). It was initially studied as a treatment for cancer but was found to have immunosuppressive properties, which led to its use as an immunosuppressive medication for autoimmune diseases. The drug was approved for use in the United States in 1998 by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (Siva et al., 2003).

Mycophenolate Mofetil (MMF) is an immunosuppressive medication that is used to prevent organ transplant rejection and to treat autoimmune diseases, such as Lupus and Inflammatory Bowel Disease (Allison and Eugui, 2000).MMF is often used in combination with other immunosuppressive drugs, such as corticosteroids, to achieve optimal results. MMF is another type of pro-drug, meaning that it needs to be converted to its active form Mycophenolic acid (MPA) to exert its intended action. Mycophenolate Mofetil (MMF) was first approved by the Food and Drug Administration (FDA) in 1995 for the prevention of organ transplant rejection (Maripuri and Kasiske, 2014). The approval was based on the results of clinical trials that demonstrated the effectiveness and safety of MMF in preventing

transplant rejection. MMF was approved as an oral pro-drug of Mycophenolic acid (MPA), which is the active form of the drug and is considered an immunosuppressive agent (Shipkova et al., 2005).

8.1.1 Mechanism of Various Purine and Pyrimidine Synthesis Inhibitors

Purine and pyrimidine inhibitors are a class of drugs that target the biosynthesis of purines and pyrimidines, which are important building blocks for DNA and RNA. By inhibiting the formation of these nucleotides, these drugs can inhibit the growth and replication of cells (Robinson et al., 2020).

8.1.1.1 Azathioprine

Azathioprine is an immunosuppressive medication that works by inhibiting the production of certain cells in the immune system, known as white blood cells. Specifically, it targets a specific enzyme called inosine monophosphate dehydrogenase (IMPDH), which is involved in the formation of purines, or important building blocks for DNA and RNA (Bremer, 2009). By inhibiting IMPDH, Azathioprine reduces the production of white blood cells, in turn, helping to reduce inflammation and the activity of the immune system (Coulthard et al., 2017). This can help treat conditions such as rheumatoid arthritis, inflammatory bowel disease, and lupus. Azathioprine is a pro-drug, meaning it is converted to its active form, 6-mercaptopurine, by the enzyme thiopurine S-methyltransferase (TPMT) to exert its action, and some patients may be deficient in this enzyme, leading to toxicity (Chouchana et al., 2012). The exact pharmacological mechanism of action for azathioprine is not fully understood; however, it is thought to involve inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is involved in the formation of purines, which are important building blocks for DNA and RNA. By inhibiting IMPDH, azathioprine reduces the production of purines, leading to a reduction in the number of white blood cells, including T-lymphocytes and B-lymphocytes, which are important cells in the immune system (Tiede et al., 2003).

The reduction in white blood cells leads to a suppression of the immune system and a decrease in inflammation. Azathioprine also has a direct effect on T-cells, as it blocks the production of interleukin-2, a key cytokine in the activation and proliferation of T-cells (Crilly et al., 1994).

8.1.1.2 Leflunomide

Leflunomide is an immunosuppressive medication that works by inhibiting the proliferation of immune cells, specifically T and B cells, which are the cells responsible for the inflammation and tissue damage seen in autoimmune diseases. Leflunomide works by inhibiting the enzyme di-hydroorotate dehydrogenase. DHODH is an enzyme that is involved in the de novo synthesis of pyrimidines, which are essential building blocks for DNA and RNA (Zhang and Chu, 2018)
Leflunomide inhibits the enzyme DHODH to block the production of pyrimidines. DHODH is an enzyme which is expressed in nearly every organ, every tissue, or even in every cell (Sykes, 2018). The activation of T-cells associated with inflammatory disorders needs to regulate through cell cycling. Leflunomide is a derivative of Isoxazol which possess a unique ability to regulate the progression through the cell cycle due to its activity of inhibition of "de-novo-pyrimidine ribo-nucleotide biosynthesis" (Breedveld and Dayer, 2000). LEF (Leflunomide) is a prodrug, and, as such, rapidly gets converted to its active metabolite A77-1726. This metabolite then inhibits the DHODH. T-cells play a very important role in the mechanism of Leflunomide as the lymphocytes gets activated and contributes to the pathologies associated with Rheumatoid Arthritis and the proliferation of T-cells gets halted by the inhibition of the synthesis of Pyrimidine (Weinblatt et al., 1999). While the exact pharmacological mechanism of action of Leflunomide is not fully understood, it is thought to involve inhibition of the enzyme dihydroorotate dehydrogenase (DHODH) involved in the de novo synthesis of pyrimidines. DHODH is the essential therapeutic target for Pyrimidine synthesis inhibition in multiple diseases. Inhibition of this enzyme causes the depletion of intracellular Pyrimidine pool (Madak et al., 2019).
This reduction in T and B cell proliferation leads to a suppression of the immune system and a decrease in inflammation. This mechanism is the reason Leflunomide

is effective in treating autoimmune diseases, such as rheumatoid arthritis and psoriatic arthritis. Leflunomide leads to the inhibition of increased concentration of plasma-TNF and Interleuukin-2. It can also decrease the number of T-lymphocytes and inhibit the production of TNF. The activation of Nuclear Factor-κB regulates the production of TNF from the lymphocytes (Imose et al., 2004).

8.1.1.3 Mycophenolate Mofetil

When MMF is converted into metabolized MPA, the depletion of the nucleosides T- and B-lymphocytes inhibits the cell-proliferation. MPA leads to the suppression of immune response and antibody formation, further inhibiting the expression of adhesion molecules and glycosylation. MPA decreases the NO-production by means of NO-Synthase. The activated macrophages produce superoxide and NO, which then generate tissue damage by combining with each other. With the help of these two mechanisms, MMF exerts anti-inflammatory activities (Allison, 2005) .
This reduction in T- and B-cell proliferation leads to a suppression of the immune system and a decrease in inflammation, which is the mechanism by which MMF can prevent organ transplant rejection and reduce the symptoms of autoimmune diseases (Shipkova et al., 2005). When MMF gets converted into Mycophenolic acid, its active form, it exerts its intended pharmacological actions.

Just like any other medication used alongside therapeutic effects, MPA shows some adverse drug reactions, such as nausea, abdominal cramps, soft bowel movements, frequent urination, vaginal itching, thrombocytopenia, and leukopenia (Epinette et al., 1987). MMF is the medication that is most widely used in organ transplants in order to prevent acute rejection, but it can cause toxicity like hematologic and gastro-intestinal tract (Mourad et al., 2001).

Initially, MMF was used to prevent acute rejection of heart, kidney and liver transplants. Later, it was used in the treatments of several other conditions, such as Systemic Lupus Erythematous. When other therapeutics failed to cure Systemic Lupus Erythematous, MMF was introduced as an effective treatment (Pisoni et al., 2005).

8.1.2 Hypothesis from Basic Science

A number of previous tranches of research on the effects on Purine and Pyrimidine Synthesis Inhibitors on the experimental animals (pre-clinical studies) can illustrate the credibility of our hypothesis regarding the meta-analysis. In order to understand the effects of drugs under this class on the levels of blood pressure, it is important to consider some previous experimental preclinical studies which suggest different results. Details can be found in **Table 8-1**.

Table 8-1 Selected previous experimental studies

Study	Design of the Study	Animal used	Result and Summary	References
Immunosuppression improves blood pressure and endothelial function in a rat model of pregnancy-induced hypertension.	Rat Model	Male (For mating purposes) and Female Sprague-Dawley rats (200-250 gms).	The results demonstrated that the medications (Azathioprine and MMF) significantly attenuated the hypertension.	(Tinsley et al., 2009)
Development of chronic allograft rejection and arterial hypertension in Brown Norway rats after renal transplantation.	Lab	Inbred male Brown Norway and six Dark Agouti rats (Harlan Sprague Dawley, Indianapolis)	The results of the study suggest that the Allograft rejection was associated with arterial hypertension. The use of medications including AZA has led to the development of hypertension.	(Vaskonen et al., 2000)
Mycophenolate mediated remodeling of gut microbiota and improvement of gut-brain axis in spontaneously hypertensive rats.	Lab	Hypertensive rats	The results of the study have indicated that MMF is not an anti-hypertensive drug but possesses antihypertensive property as it helps to lower down the blood pressure.	(Robles-Vera et al., 2021)
Cardio-tropic Influence of Synthetic And Genetically-Engineered Suppressors in Rats With Experimental Rheumatoid Arthritis Combined With Arterial Hypertension.	Animal study	Mature non-linear white rats of both sexes.	The study has indicated that Leflunomide, when given in combination with Etanercept, did not prompt any changes in the blood pressure in case of adjuvant arthritis.	(Seredynska et al., 2020)

8.1.3 Rationale of the Study

A range of eminent studies exist which have already discussed the effects of these medications cause risk of hypertension. For an example, in a clinical study of Rozman et al. (2002), their study investigated that Leflunomide a DMARD (Disease-Modifying Anti-rheumatic Drugs) when used to treat Rheumatoid Arthritis led to an increase in the levels of blood pressure as a side effect. In the current study there was limited evidence to justify that the relation of hypertension was not related to renal impairment and proteinuria. The up regulation in the levels of blood pressure wasn't studied in detail. This study, by comparison, suggests that medication can be responsible for the up-regulation of the blood pressure.

van Riel et al. (2004), while assessing the safety profile of the drug Leflunomide for the treatment of Rheumatoid Arthritis, suggested that the medication aggravated the levels of blood pressure in those with pre-existing hypertension and new-onset of hypertension was also observed to be present.

In order to understand the effects of drugs under this class on the risk of hypertension, it is crucial to consider a range of previous experimental clinical studies, particularly those that suggests different results, these are mentioned in **Table 8-2.**

Table 8-2 Selected previous clinical studies

Therapy	Study	Design of the Study	Patients	Follow-up Period	Intervention	Result/ Summary	References
Azathioprine	Circadian variations of blood pressure and heart rate early and late after heart transplantation.	Case study	62 patients	12 months	For heart transplantation, Azathioprine is given as an immunosuppressive drug to the patient.	As a result of undergoing immunosuppressive therapy, the patient experiences the return of normal blood pressure and reappearance of the blood pressure in early and late after heart transplantation.	(Bracht et al., 1996)
	Posterior Reversible Encephalopathy Syndrome and Azathioprine.	Case report	1 patient	4 weeks	medicated with Azathioprine 125 mg/day for 1 month	After being treated with azathioprine, patient complained of headache and palinopsia of 1 weeks' duration presenting with high blood pressure of 200/100 mm Hg. As a result, azathioprine is unable to treat hypertension.	(Vilas-Boas and Corte-Real, 2019).
Leflunomide	Onset of Hypertension in Leflunomide	Case-Control Study	144 patients	- 240 weeks.	The patients treated with Leflunomide had	The administration of the Leflunomide was	(Ishaq et al., 2019)

	Treated Low Socioeconomic Rheumatoid Arthritis Patients: an Unseen Iceberg.				developed a high blood pressure level compared to the second drug-treated group.	found to increase the systolic blood pressure. The Asians were higher risk of the development of hypertension when compared to other populations.	
Mycophenolate mofetil	Influence of the new immunosuppressive combinations on arterial hypertension after renal transplantation.	Case Study.	Patients after renal transplantation.	-	Mycophenolate Mofetil could reduce the incidence of post-transplant arterial hypertension.	The combination of Mycophenolate-mofetil in a triple therapy regimen caused reduction in the levels of blood pressure in patients with hypertension either by discontinuing of Steroids or reduction in the dose of CsA.	(Morales, 2002).
	Mycophenolate Mofetil can be used as mono-therapy late after liver transplantation.	Prospective study	50 adult patient's with liver transplant	336 weeks.	Mycophenolate mofetil shows improvement in arterial hypertension.	There was no significant difference in mean systolic blood pressure and mean diastolic blood pressure at any time during the study after 12 and 18 months.	(Planas et al., 2004).

8.2 Methodology

8.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

8.2.2 Data extraction

The initial search yielded 1,168 articles using the search strategies detailed in the Appendix A, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of the research accordingly **(**see **Figure 8-1).**

After accounting for and removing duplication, the remaining 712 citations or abstracts were assessed for inclusion criteria. At that point, 627 articles were eliminated based on a title and abstract review process, approximately 54% of the total, as predefined by the PICOS criterion. Of the 85 publications that remained eligible, fifty-seven were eliminated after a full-text screening for several reasons which are described in **chapter 3,Table 3-1**. Ultimately, twenty-eight trials with 9,034 patients enrolled for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

8.2.3 Description of excluded studies

A total of fifty-seven publications were excluded after an extensive eligibility check of their full text. Nine studies (Galiatsou, Ishaq, Kaltwasser, Ying, Kumar , Heckmann Pelletier, Vera and Schnuelle) were removed for having a different design, each of them not randomized control trials.

Two studies (Gipson and Hocker,) were excluded on account of the participants being children which was criteria for exclusion in my considerations. Eight studies (CAESAR, Kobashigawa, Lee, Wu J, Manousou ,Mohammadi, Nakache and Rostaing) used different medications which not related to our medications.

One study (Maes) which patients are treated with antihypertensive drugs. Two studies(Samonakis and Mok, C. C.) were excluded due insufficient results, which were abstract.

The most excluded type of studies were reported to have different outcomes, which did not mention hypertension (HTN), in addition to studies that used same medication in both arms. in **chapter 3,Table 3-1** summarises the reasons for the elimination of each trial.

8.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.
Sensitivity analyses were completed by the exclusion of trials with [1] poor methodological qualities; [2] small sample sizes with less than 100 total participants; and [3] studies not crossing Cl 95%.

Subgroup analyses for Purine and Pyrimidine inhibitors were performed as follows: (1) comparator drugs; (2) clinical setting; (3) duration of follow-up.

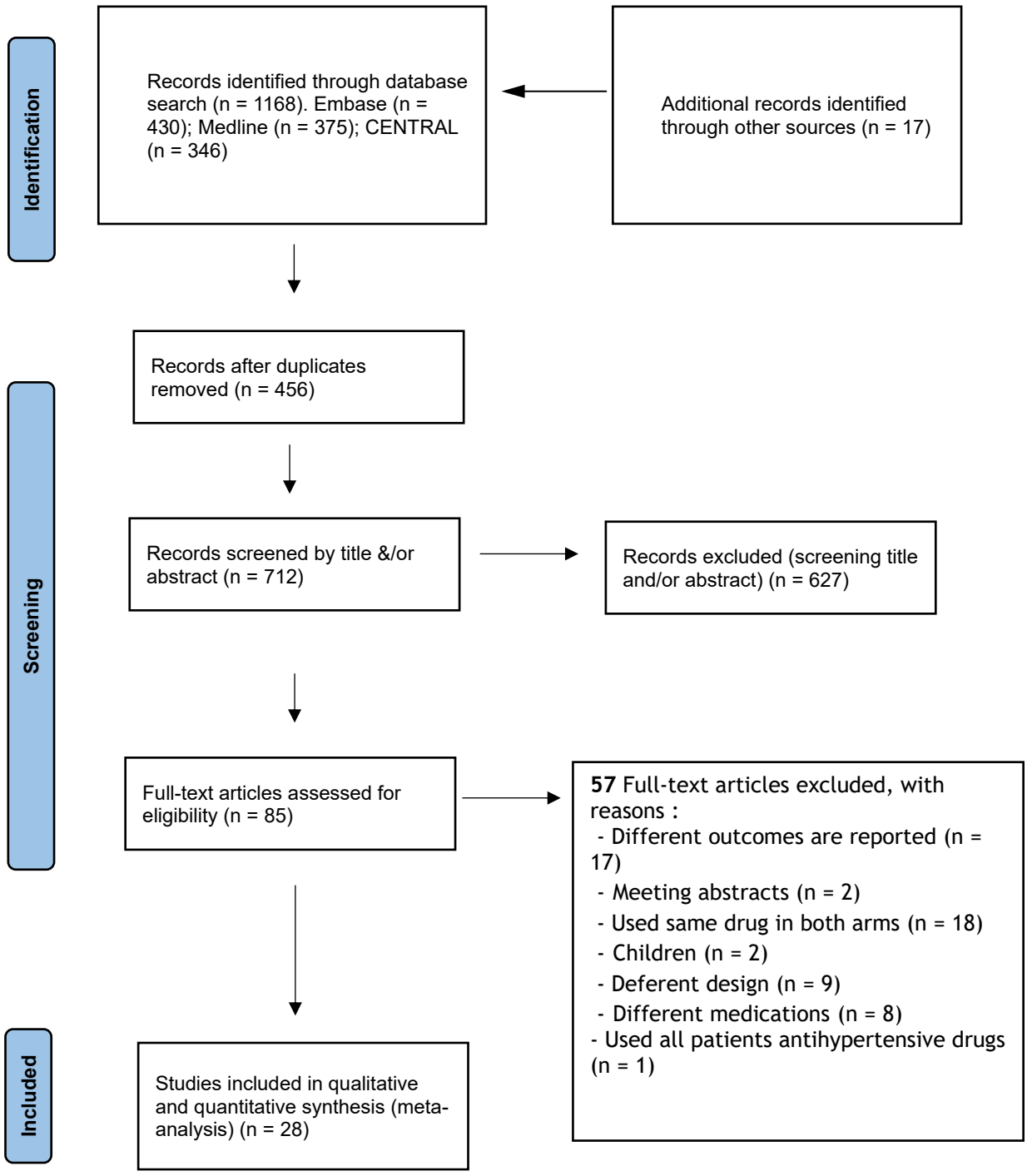

Figure 8-1 PRISMA Study flow diagram

8.3 Results

In total, twenty-eight eligible Purine and Pyrimidine inhibitors trials with 9,043 patients were enrolled, with an average follow-up period of 1 years (range three months to five years).
The average patient age for all trials was forty-nine years old.
Figure 8-1 provides a summary of the trial searching and identification process.
Fifty-seven studies were excluded for logical reasons.
Table 3-1 in chapter 3 records the reasons for the excluded studies and twenty-eight RCTs (randomised controlled trials) were used for the final review.

The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

The majority of studies were published since 2000. However, there is one study from the nineteen-eighties (Najarian), published in 1985. The study compared Azathioprine with Cyclosporine which prednisone been added in both groups; two hundred thirty patients reported hypertension and other conditions as incidence.

Two studies were published in the nineteen-nineties such as Smolen and Strand, which both published in 1990, Smolen study investigated the effect of Leflunomide they used three arms which they compared leflunomide with placebo and sulfasalazine in 358 patients. Strand's study compared three arms, which were leflunomide compared with placebo and Methotrexate in 482 patients. In both studies, all patients were diagnosed with rheumatoid arthritis and reported a number of patients who experienced adverse effects, one of them hypertension.

The Kahan study was the sole study published in 2000 that contributed to the safety and efficacy of both Sirolimus and Azathioprine drugs on patients with acute renal allograft rejection.

Two studies (Mimouni and Schiff) were published in 2010. Mimouni study compared Myclophenolate mofetil with placebo which Prednisone was combined with Myclophenolate mofetil, for Treating Pemphigus Vulgaris patients. Schiff's study

also compared Myclophenolate mofetil with placebo for patients had rheumatoid arthritis.

The majority of included RTCs compared Purine and Pyrimidine inhibitors to active controls involving group of Calcineurin inhibitors, Mthylprednisolone and Sirolimus. Some of these were divided into subgroups **(**See **Figure 8-7)** and others were not recategorized because each drug had only one study, which cannot be used for the purposes of meta-analysis.

Most of the studies employed a double-blind design except for eight (Beissert, Karanikolas, Simone, Sticherlines, Sundel, Takesashi, Vitko and Yunyun) who used an open-label design. Five studies (Gheith, Loannides, Kahaly, Metzler and Najarian) did not specify the nature of the design whether it was open or double-blind. None of the studies implemented a factorial design.

The follow-up study periods were at least three months, while the most extended period was more than four years. All the study participants were adults with a mean age of over forty-five years old. All participants in the studies were male and female but differ in proportion from study to study.

The patients have been diagnosed with autoimmune diseases. Most studies diagnosed rheumatoid arthritis, except some studies which reported thatpatients were diagnosed with other autoimmune diseases such as, chronic plaque psoriasis, liver and kidney transplantation, pemphigus vulgaris, Renal allograft rejection, Wegener's granulomatosis, Systemic lupus erythematosus, immunoglobulin g4 disease and Graves' orbitopathy. All the relevant details are described in **Table 8-3**.

Table 8-3 The underlying disease of each trial

Trial	Background disease	Trial	Background disease
Beissert 2009	chronic plaque psoriasis	Kahan 2000	Renal allograft rejection
Kremer 2004	rheumatoid arthritis	Karanikolas 2006	rheumatoid arthritis
Schiff 2010	rheumatoid arthritis	Metzler 2007	Wegener's granulomatosis
Smolen 1999	rheumatoid arthritis	Najarian 1985	renal allografts
Strand 1999	rheumatoid arthritis	Silva 2007	Renal Transplantation
Becker 2008	Liver Transplantation	Sticherlims 2017	bullous pemphigoid
Boudjema 2011	Liver Transplantation	Sundel 2011	Systemic lupus erythematosus
Simone 2009	Liver Transplantation	Takasashi 2013	Renal Transplantation
Emery 2000	rheumatoid arthritis	Vitko 2006	Kidney Transplantation
Gheith 2007	Kidney Transplantation	Yunyun 2019	immunoglobulin g4 disease
Ioannides 2012	pemphigus vulgaris	Kahaly 2018	Graves' orbitopathy
Ishaq 2011	rheumatoid arthritis	Belani 2022	rheumatoid arthritis

Purine and Pyrimidine inhibitors were compared to a placebo in five studies which included 1748 patients and to other active drugs in 23 studies which included 7295 patients. A total of 50 (4.1%) and 16 (3%) events occurred in Purine and Pyrimidine inhibitors and the placebo groups. The risk of hypertension was higher in Purine and Pyrimidine inhibitors than the placebo group although the risk ratio was not statistically significant (RR = 1.37, 95% CI 0.78; 2.44, P = 0.28). Indeed, no heterogeneity was observed between studies (I^2 = 0%, P = 0.96) indicating that the variability in effect sizes between studies is derived by chance (P > 0.05).

A total of 697 and 971 events occurred in Purine and Pyrimidine inhibitors and the active drug groups, respectively. The risk of hypertension was significantly lower

in Purine and Pyrimidine inhibitors than other active drugs (RR = 0.81, 95% CI 0.65; 0.99, P = 0.04) favoring Purine and Pyrimidine inhibitors. Gheith and Becker studies contributed to 10.7% and 10.8% of the meta-analysis weight. The risk of hypertension was significantly higher in Purine and Pyrimidine inhibitors than the active drug in Emery study while the opposite was observed in four studies which are Kahan, Najarian, Vitko and Schiff. The effect size was not statistically significant in any of the remaining studies. Substantial heterogeneity was observed between studies (I^2 = 76%, P = 0.00001) (See **Figure 8-2**).

Similar results were observed when the fixed effects model was used for the analysis(**Figure 8-3**). The risk of hypertension was not significantly different between Purine and Pyrimidine inhibitors and the placebo groups (RR = 1.39; 95% CI 0.79; 2.47, P = 0.25). Schiff study contributed to approximately one-third of the meta-analysis (32.7%). The risk of hypertension was significantly lower in Purine and Pyrimidine inhibitors than other active drugs supporting the results produced by the random-effects model (RR = 0.79, 95% CI 0.73; 0.85, P = 0.00001). Becker and Gheith studies were assigned the highest weights, respectively (25.1% and 19.3%).

Appendix D, Figure D-5 shows the distribution of the 23 studies presented in a funnel plot. Missing studies can be seen at the top and bottom left of the plot, while three outlier studies can be observed, Emery, Najarian and Schiff. The asymmetrical appearance of the funnel plot suggests the possibility of publication bias or other forms of bias in the included studies.

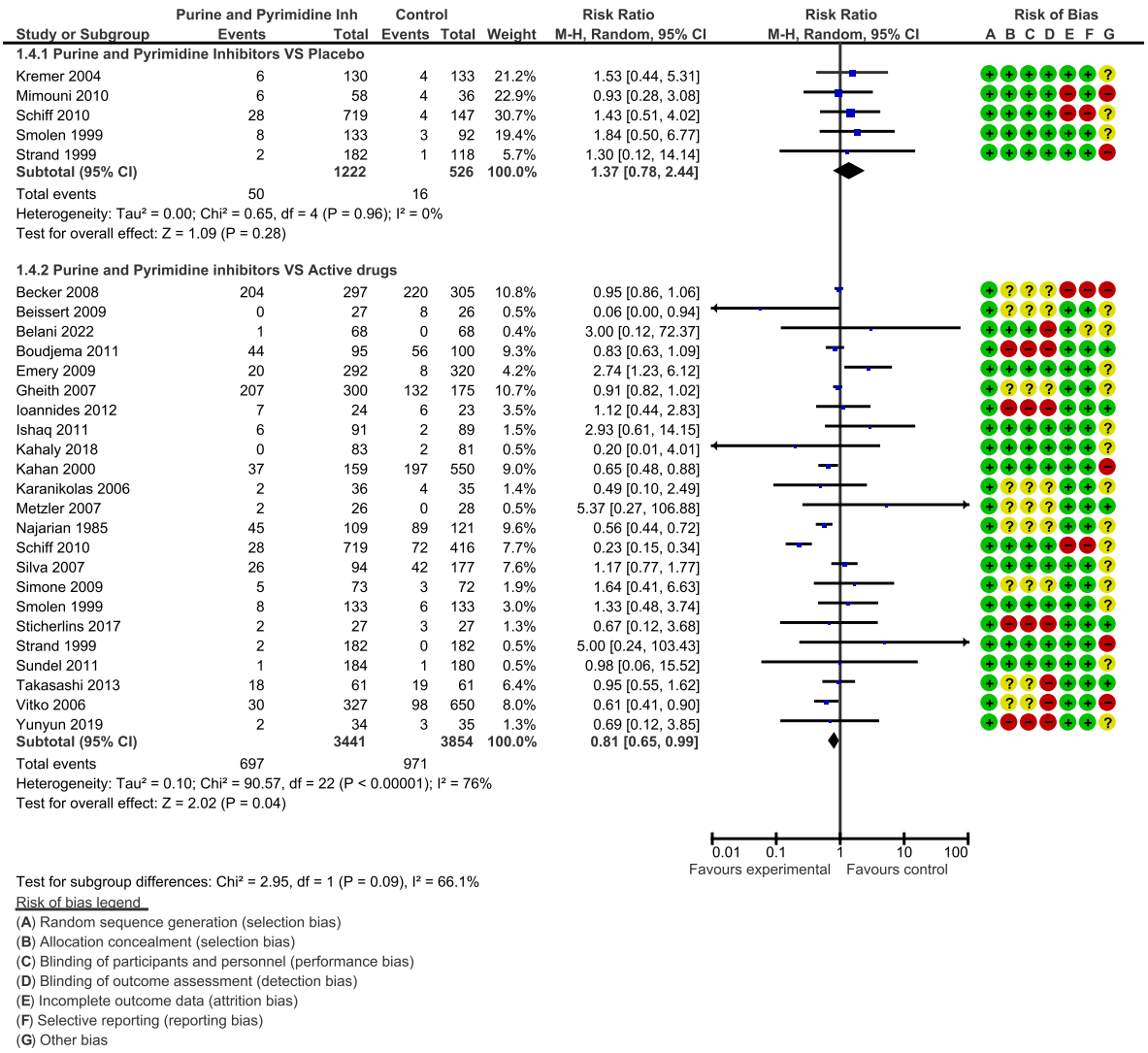

Figure 8-2 Random effects model for the association between Purine and Pyrimidine inhibitors and the risk of hypertension.

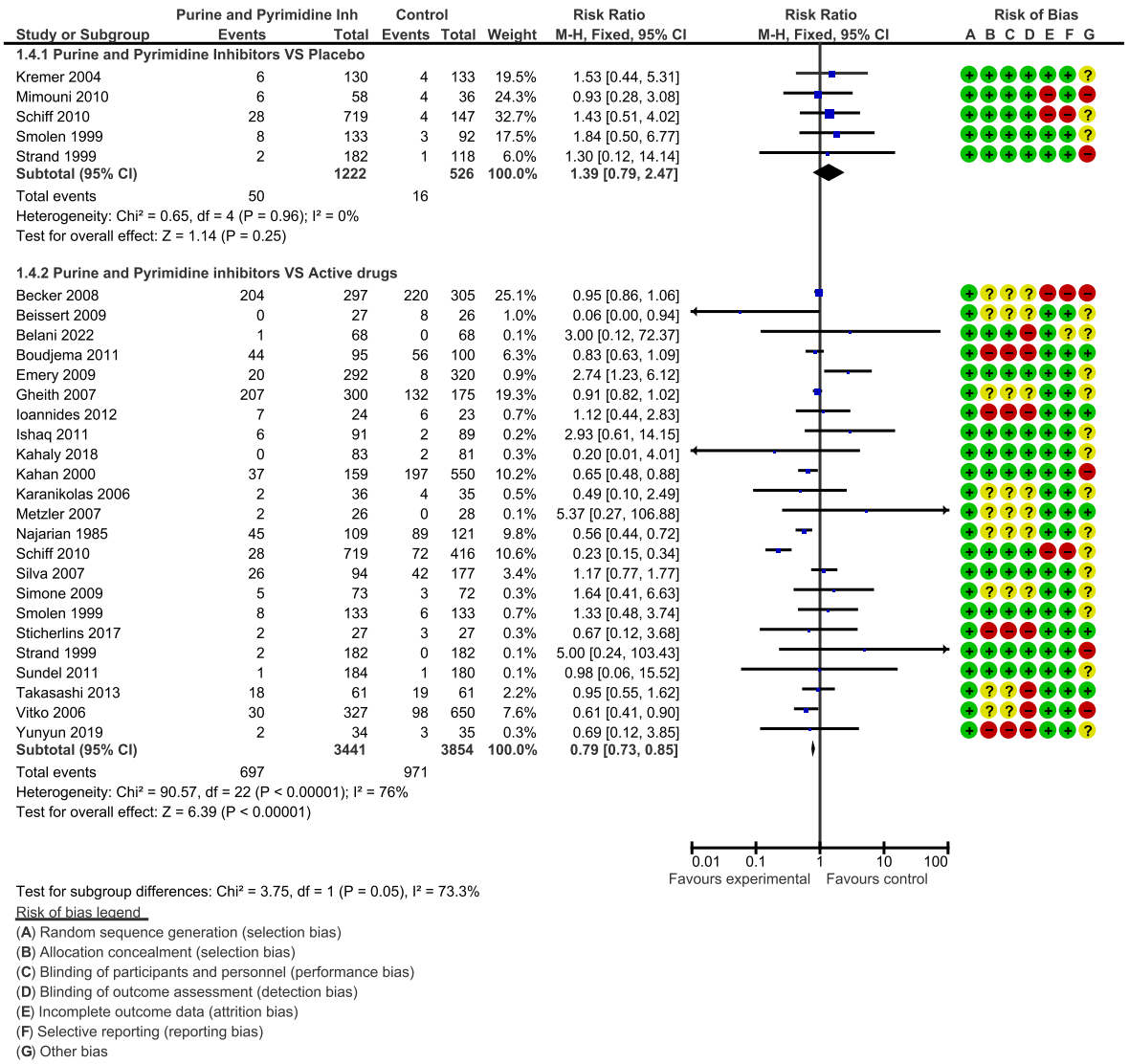

Figure 8-3 Fixed-effects model for the association between Purine and Pyrimidine inhibitors and the risk of hypertension.

8.3.1 Sensitivity analyses

Sensitivity analysis was performed to assess the robustness of estimates. The association between the use of Purine and Pyrimidine inhibitors and the incidence of hypertension was evaluated after excluding (1) studies with a high risk of bias; (2) studies with a small sample size; and (3) studies not crossing 95% CI.

As **Figure 8-4** shows, sixteen studies were included in meta-analysis after the exclusion of twelve studies, which had a high risk of bias. A not statistically significant association was observed between the use of Purine and Pyrimidine inhibitors and the risk of hypertension (RR = 0.85, 95% CI 0.59; 1.24, P = 0.40). A total of 387 and 654 events occurred in Purine and Pyrimidine inhibitors and the control group, respectively. High heterogeneity was observed between studies (I^2 = 82%, P = 0.00001).

One study with small sample sizes were excluded in the placebo arm and thirteen in the active drugs subgroup arm. Similar estimates were obtained when Purine and Pyrimidine inhibitors was compared with the placebo arm (RR = 1.54, 95% CI, 0.80; 2.96, P=0.19). This indicated that the risk of hypertension was not significantly different between Purine and Pyrimidine inhibitors and the placebo arm. The risk of hypertension was still lower in Purine and Pyrimidine inhibitors than in other active drugs when twelve studies with a small sample size were excluded (RR = 0.73, 95% CI, 0.55; 0.98, P=0.03)**(**See **Figure 8-5).**

Twelve studies were excluded because they did not meet the 95% confidence interval, included fifteen studies in the analysis. After exclusion, the estimate from the RE model was not statistically significant, which was (RR = 0.93, 95% CI, 0.87; 1.00, P = 0.06). A total of 511 events in 1714 total and 457 events in 1526 total occurred in the purine and pyrimidine inhibitor and comparator groups, respectively. No heterogeneity was observed between the studies which was (I^2 = 0%, P = 0.86) **(**See **Figure 8-6).**

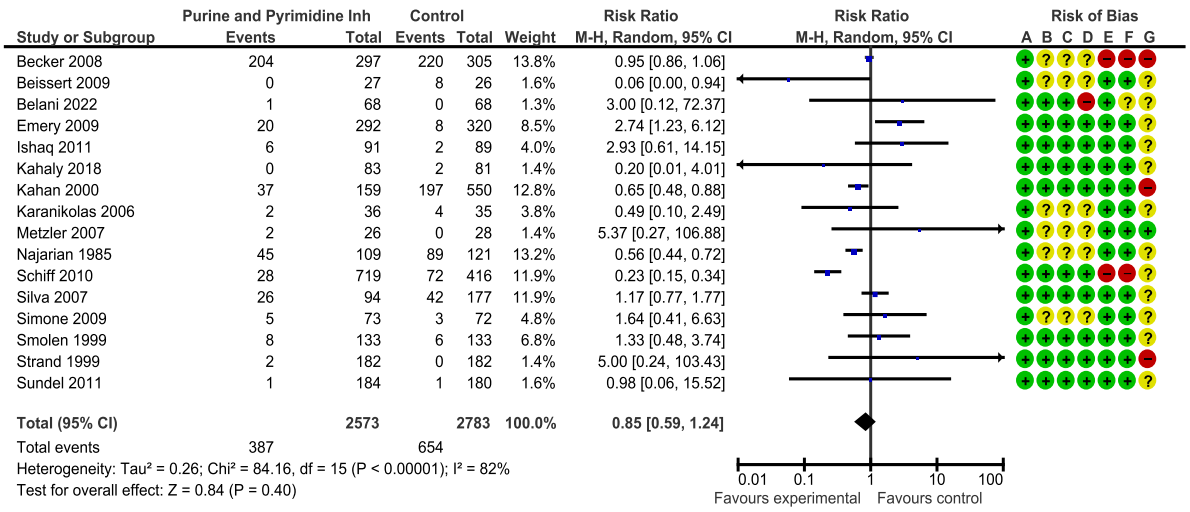

Figure 8-4 Sensitivity analysis for the association between Purine and Pyrimidine inhibitors and the risk of hypertension. (RE model) after excluding studies with high risk of bias were excluded.

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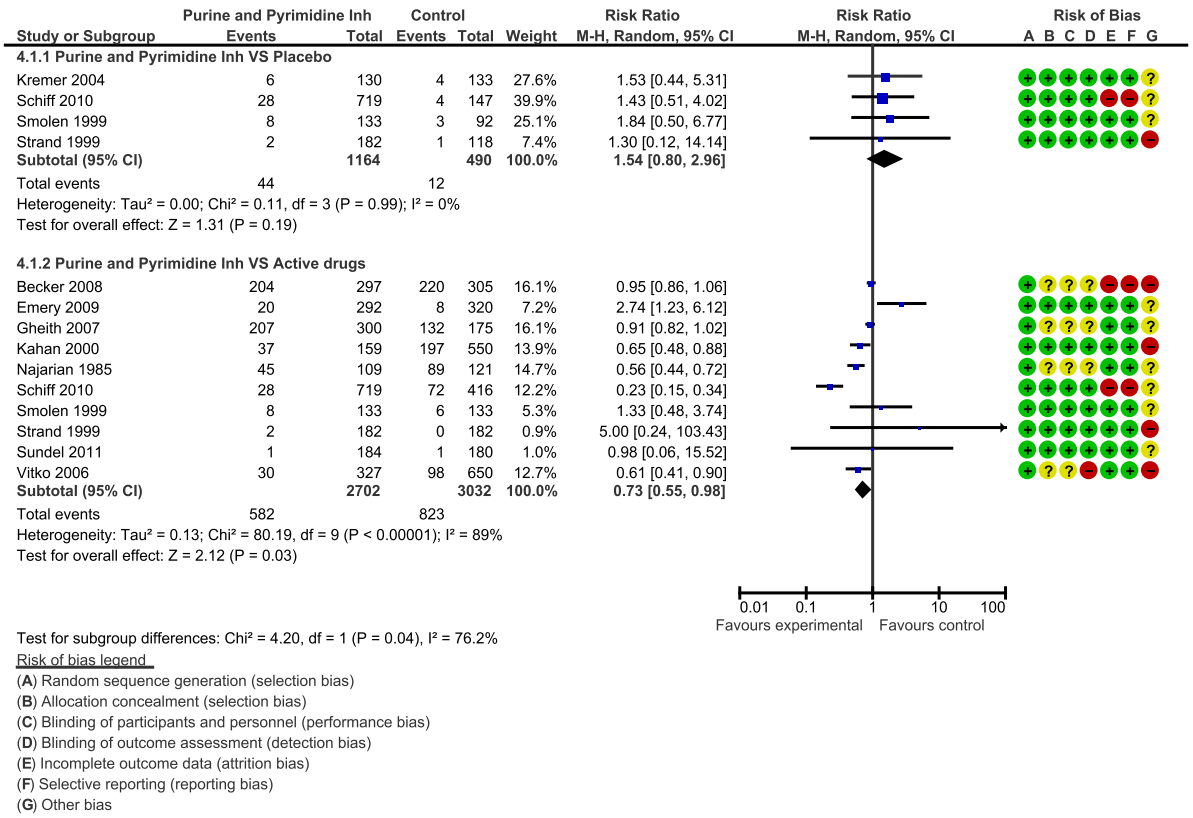

Figure 8-5 Sensitivity analysis for the association between the use of Purine and Pyrimidine inhibitors and the risk of hypertension (RE model) after excluding studies with a low sample size.

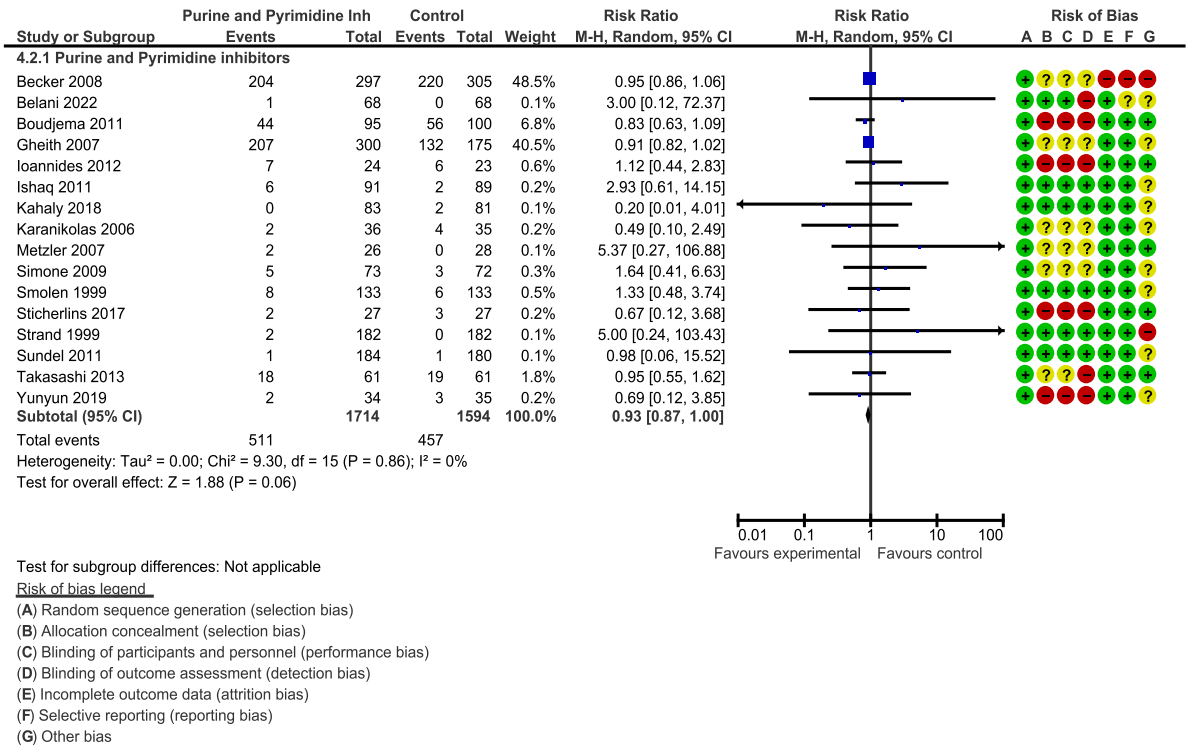

Figure 8-6 Sensitivity analysis for the association between the use of Purine and Pyrimidine inhibitors and the risk of hypertension (RE model) after excluding studies not cross 95% confidence interval.

8.3.2 Subgroup analyses

Table 8-4 summarises the subgroup analyses of Anti-IL17s' impact on hypertension risk.

The analysis, which included active drugs, was stratified by the type of comparator into three different subgroup analyses.

The RE model revealed a statistically significant lower risk of hypertension in Purine and Pyrimidine inhibitors than Calcineurin inhibitors (RR = 0.80, Cl,0.66; 0.99, P = 0.04). A total of 828 cases and 727 controls were included in the analysis, with five hundred and five hundred-five events, respectively, with substantial

heterogeneity observed between studies (I^2 = 80%,P = 0.0004). The Becker study provided the highest weight (29.2%).

When the RE model was used to compare Purine and Pyrimidine inhibitors to Methylprednisolone, a risk ratio was not statistically significant (RR = 0.90, 95% CI, 0.41; 1.97, P = 0.79). No heterogeneity was observed between studies (I^2 = 0%,P = 0.51). Ioannides study contributed to 72.3% of the meta-analysis weights.

Two studies compared Purine and Pyrimidine inhibitors to Sirolimus, 486 and 1200 in Purine and Pyrimidine inhibitors and the control groups, respectively. The RE model revealed a significantly lower risk of hypertension in Purine and Pyrimidine inhibitors than in the Sirolimus (RR = 0.63, 95% CI, 0.50; 0.80, P = 0.0002). No heterogeneity was observed between studies (I^2 = 0%,P = 0.79)**(**see **Figure 8-7).**

Only four studies included patients with HTN at baseline **(Figure 8-8)**. The pooled estimate from the RE model was not statistically significant (RR = 0.84, 95% CI, 0.65; 1.09, P = 0.19). The remaining nineteen studies included patients with no HTN at baseline. The pooled estimate revealed a risk ratio that was not statistically significant (RR = 0.93, 95% CI, 0.74; 1.16, P = 0.51). Moderate to substantial heterogeneity was observed between studies in both subgroups which was (I^2 = 50% and I^2 = 53%).

The follow-up duration was under two years in nineteen studies and two years or more in the remaining four studies. When the analysis was stratified by treatment duration, no association was observed between the use of Purine and Pyrimidine inhibitors and the risk of hypertension in patients followed up for under two years (RR = 0.91, 95% CI 0.78; 1.07, P = 0.27), and those followed up for two or more years (RR = 0.83, 95% CI 0.53; 1.32, P = 0.44). For the first subgroup, 3,034 and 3,207 patients were included in Purine and Pyrimidine inhibitors and control groups, with low heterogeneity observed between studies (I^2 = 26,P = 0.14). For the second subgroup, 568 and 416 patients were included in the Purine and Pyrimidine inhibitors and the control groups. However, in this case, substantial heterogeneity was observed between studies (I^2 = 81,P = 0.001) (See **Figure 8-9**).

Table 8-4 The Summary of a meta-analytical subgroup analysis by RE model demonstrates the effect of Purine and Pyrimidine inhibitors compared with control (placebo and active) on the risk of hypertension.

Subgroup analysis		**Studies**		**Participant**	**event**	**Hypertension Incidence (%)**		**RR (M-H, Random, 95% CI)**	**P value***	**I^2 (%)**
						Intervention	Control			
Overall	RE	Placebo	5	1748	66	4.09	3.04	1.37 [0.78,2.44]	0.28	0
		Active drugs	23	7295	1668	20.25	25.19	0.80 [0.65,0.99]	0.04*	77
Type of comparator	Calcineurin Inhibitors		5	1555	1005	60	69	0.80 [0.66,0.99]	0.04*	80
	Methylprednisolone		3	280	20	6.38	7.91	0.90 [0.41,1.97]	0.79	0
	Sirolimus		2	1686	362	13.78	24.58	0.63 [0.50,0.80]	0.0002*	0
Clinical setting	Hypertension at baseline**		4	1451	618	45	41	0.84 [0.65,1.09]	0.19	50
	No hypertension at baseline**		20	5733	990	14.64	20.10	0.93 [0.74,1.16]	0.51	53
Duration of follow-up	Less than two years**		19	6241	1124	14.73	21.11	0.91 [0.78,1.07]	0.27	26
	Two years Or Longer**		4	984	486	46	54	0.83 [0.53,1.32]	0.44	81

† **list of definitions and abbreviations**: CI: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant.; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity.;** Placebo and active drugs have been combined.

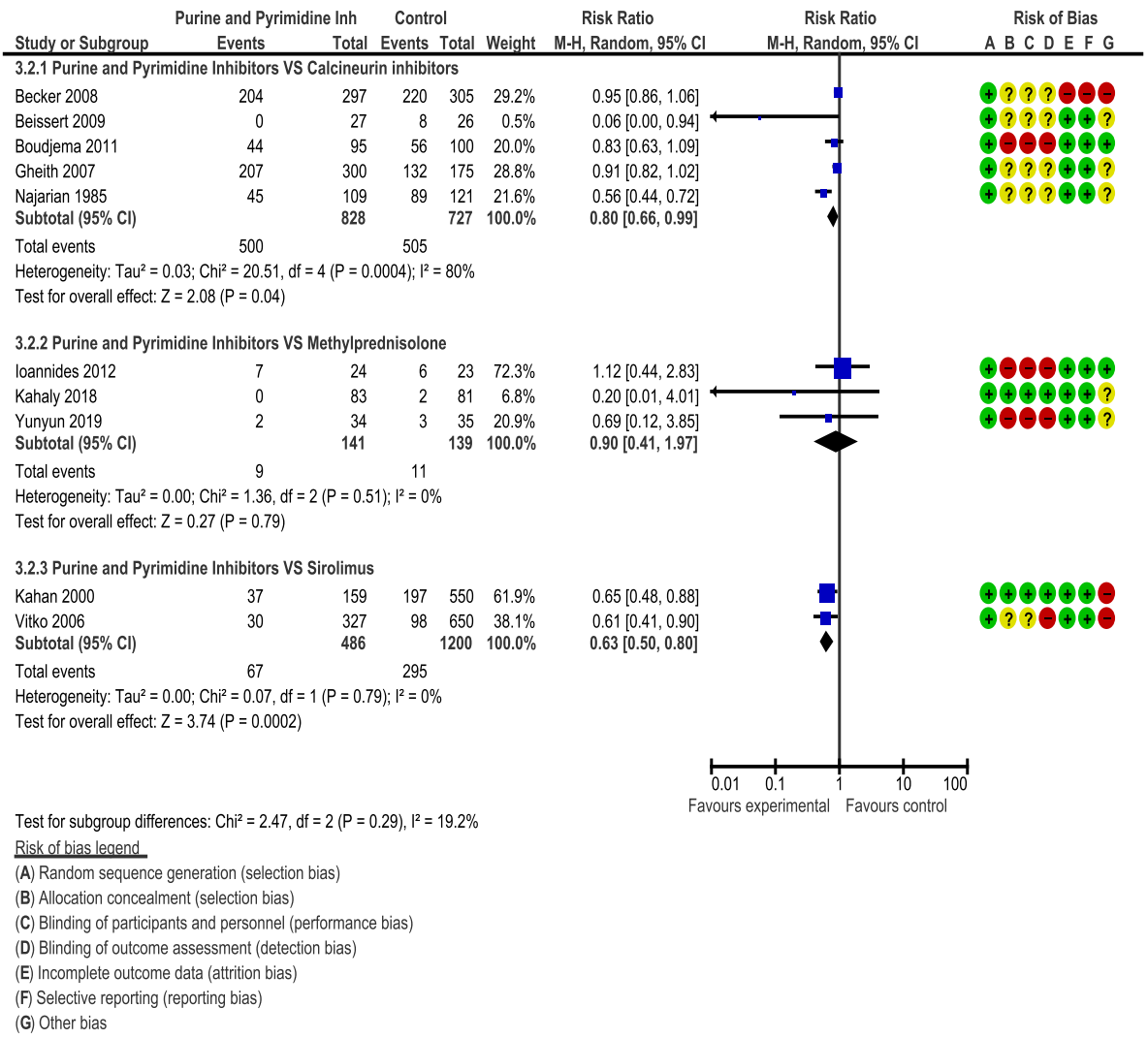

Figure 8-7 Subgroup analysis for the association between Purine and Pyrimidine inhibitors and the risk of hypertension. (The analysis was stratified by the type of comparator).

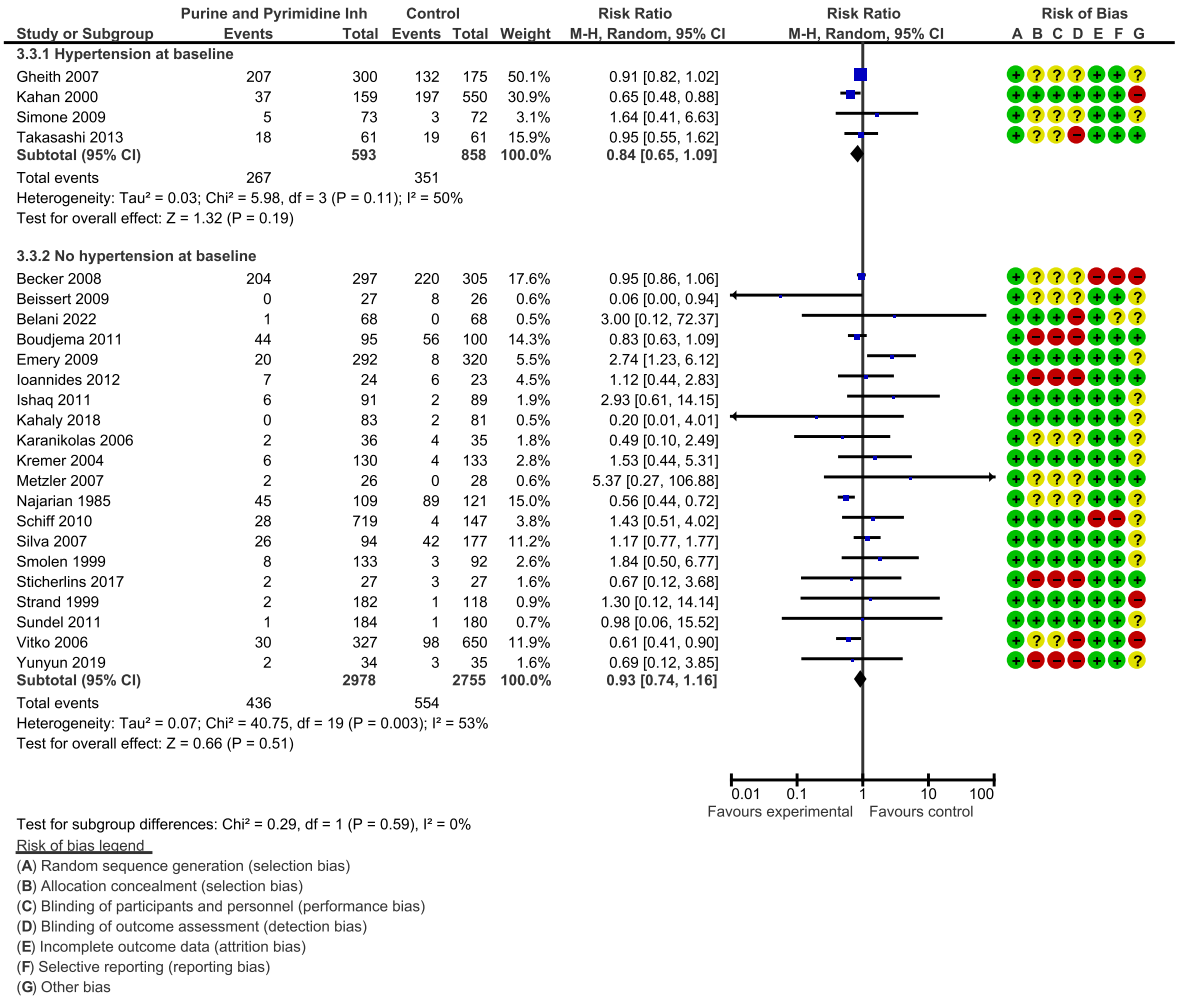

Figure 8-8 Subgroup analysis for the association between Purine and Pyrimidine inhibitors and the risk of hypertension. (The analysis was stratified by clinical population setting. Placebo and active groups were combined).

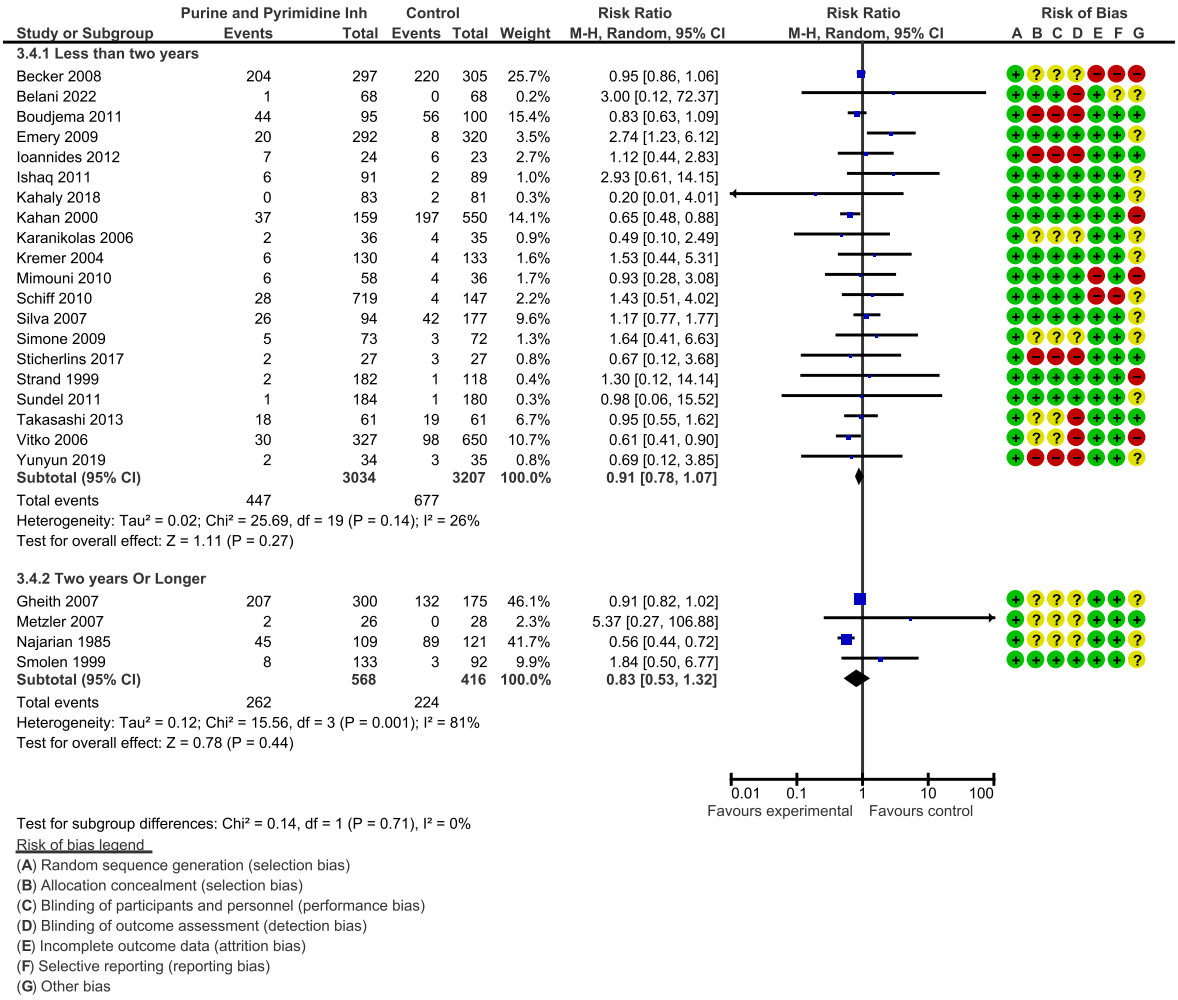

Figure 8-9 Subgroup analysis for the association between Purine and Pyrimidine inhibitors and the risk of hypertension. (The analysis was stratified by the duration of follow-up. Placebo and active groups were combined).

8.4 Discussion

The final outcomes of the study indicated that in our meta-analysis of hypothesis the same inhibitors of the synthesis of Purine and Pyrimidine do not cause any risk of hypertension when they were compared to the placebo group. Nonetheless, this showed a reduction to these levels when was compared to the other active drugs. Purine and Pyrimidine synthesis plays a huge role in physiological system of our immune system. Purines and pyrimidines are types of nitrogenous bases that are found in DNA and RNA.

A research study found that a randomized trial of Boudjema et al. (2011) conducted on the usage of Mycophenolate Mofetil and some other drugs for Liver Transplant. In this randomized clinical trial, the researchers attempted to reduce the adverse drug events which were suspected to occur by these medications. These adverse events included renal dysfunction, arterial hypertension, risk of diabetes, and acute graft rejection. The main focus of this study is the hypertension, which demonstrates that the drug caused the reduction in the incidence of Arterial Hypertension. From this study it can be concluded that Mycophenolate Mofetil do not cause risk of hypertension but these effects need to be investigated further as some studies have showed that this medication reduced the risk of hypertension.

In a research of Herrera et al. (2006) the same drug Mycophenolate Mofetil was used to treat inflammatory disorders, Rheumatoid Arthritis and Psoriasis, on experimental rats. In this study this is used to improve the risk of hypertension associated with the treatment. The study suggested that infiltration of inflammatory cytokines and then oxidative stress leads induced hypertension. The reduction in various biomarkers had a direct correlation with the levels of blood pressure. Data from the study provides significant justification to our hypothesis that this medication can reduce the risk associated with hypertension.

In a study done by Dudley et al. (2005) the Mycophenolate Mofetil was used as a regimen with Cyclosporine A for the treatment of Renal Allograft Recipient with abnormalities with Renal Toxicity secondary to Chronic Allograft Nephropathy for their immunosuppressive activity. This treatment was followed by the withdrawal

of Cyclosporine A. This was the first randomized, controlled trial to demonstrate the Cyclosporine-A withdrawal in the presence of Mycophenolate Mofetil in renal function. The study has mentioned that a number of factors can be responsible for the development of this condition along with hypertension and nephrotoxicity. A range of laboratory parameters were analysed including blood pressure. The result of this study has suggested that the risk of hypertension was decreased.

In our comprehensive meta-analysis findings, purine and pyrimidine synthesis inhibitors were compared to placebo, and active drugs showed different results. In the comrison of Purine and Pyrimidine Synthesis inhibitors and the placebo the estimation from the effects showed that the risk ratio was not statistically significant and the results of this comparison were (RR = 1.37, 95% CI 0.78; 2.44, P = 0.28). In the same way, the risk of hypertension was significantly lower in the Purine and Pyrimidine synthesis inhibitors group than in that for other active drugs and results of this comparison were: (RR = 0.81, 95% CI 0.65; 0.99, P = 0.04).

The study outcomes were different in another comparison when active drugs were stratified by the comparator type in the three different subgroups. With the first comparator that is Calcineurin inhibitors, the risk was significantly lower in Purine and Pyrimidine synthesis inhibitors while the results of this comparison were (RR = 0.80, 95% CI, 0.66; 0.99, P = 0.04). When the inhibiotrs of Purine and Pyrimidine synthesis were compared to Metylprednisolone, the risk of hypertension wasn't different between the groups and the results were (RR = 0.90, 95% CI, 0.41; 1.97, P = 0.79).The final comparison was conducted between Purine and Pyrimidine synthesis inhibitors and Sirolimus. The risk of hypertension with Purine and Pyrimidine synthesis inhibitors were significantly lower than Sirolimus and the results obtained were (RR = 0.63, 95% CI, 0.50; 0.80, P =0.0002).

However, there are a number of previous studies which support our hypothesis and the results of our study. The results of these studies vary with the type of study and also the amount of dose received and the state of the subjects as in healthy or in any diseaased state.

The study mainly suggested that when these medications were compared to a placebo, the comparators showed different results. In the other comparison, Purine and Pyrimidine Synthesis Inhibiotrs were compared to the active drugs to analyse their risks with hypertenison and the risk of hypertension being statstically lower in Purine and Pyrimidine Synthesis Inhibiotrs. The active drugs were stratified by the type of comparator into three different subgroup analyses. In the first analysis done between Calcineurin and Purine and Pyrimidine Synthesis Inhibitors, the risk of hypertension was lower in the inhibitors of Purine and Pyrimidine. In the second analysis the comparison that was made between Purine and Pyrimidine Synthesis Inhibiotrs and Metylprednisolone, there was no risk of hypertension associated. In the final comparison that was made between these inhibitors and Sirolimus, there was statsically lower in Purine and Pyrimidine Synthesis Inhibitors. All these results needs to be re-investigated and while doing the research a number of factors should be taken in account for clear and complete justification.

In a meta-analysis done by,Golicki et al. (2012) ,Leflunomide was evaluated for its efficacy and safety by comparing it with Sulfasalazine and Methotrexate. The usage of leflunomide monotherapy was proved to be more effective than others. Leflunomide also led to relieve the symptoms and signs of Rheumatoid Arthritis. In this meta-analyisis Leflunomide, when compared to Methotrexate, caused higher risk of hypertension and other associated abnormailities. This result indicates that leflunomide can cause an elevation in hypertension when used to treat Rheumatoid Arhtiritis.

In another meta-analysis done by Cao et al. (2019) to evaluate the effects of Mycophenolate Mofetil on the blood pressure have identified that it can reduce the various adverse effects including hypertension. In their study they have mentioned that MMF can attenuate risk of hypertension, but their study clearly suggests that Mycophenolate Mofetil can cause a slight decrease in diastolic blood pressure.

Another study by Li et al. (2004) has suggeted that when the medications like NSAIDs (Non-Sterioidal Anti-Inflammatory Drugs) and DMARDs were used to treat

the Rheumatoid Arthritis and control the inflammation. These medications cause some toxicities and one of them was hypertension. The DMARD used here was Leflunomide which is a pyrimidine synthesis inhibitor. In this study there were a number of drug-related adverse effects associated with Leflunomide and one of them was hypertension. Hence, as a result this study has clearly indicated that Leflunomide can increase the risk of hypertension in humans.

In a study done by Gordjani et al. (1990) suggested that the hypertension associated with Renal Transplantation can be treated using Azathioprine and Cyclosporine. The study suggested that the main concern here was persistent hypertension with complications such as cerebrovascular and cardiovascular complications. The central focus of the study was on the investigation of incidence to find out the root cause of the risk hypertension development associated with these medications. The results of the study suggested that the main cause of hypertension was cyclosporine which indicates that the treatment with Azathioprine did not cause any elevation on the risk of hypertension. According to the research, the use of Azathioprine could cause any complication. Hence it can be concluded that this medication does not cause any elevation.

From the above data, it can be concluded that the medications under Purine and Pyrimidine synthesis inhibitors demonstrate different effects on the risk of hypertension. Some studies indicate that some medications increase and decrease the risk of hypertension. There were four studies which indicated that Mycophenolate Mofetil led to a decrease the risk of hypertension. The studies related to Azathioprine showed no elevation in the risk of hypertension in their results. These results could not give a full explanation to the effects of these on Hypertension. Another medication, Leflunomide, was shown to increase the risk of hypertension in all the studies which lends a fair conclusion that these medications increase the risk of hypertension. In case of Azathioprine and Mycophenolate Mofetil there is no clarity in their case so it can be justified by the factors. These factors can influence this outcome. The first factor depends upon the comparison made between Purine and Pyrimidine synthesis inhibitors, and other drugs showed no difference in their results. In our meta-analysis, the

comparison of purine and pyrimidine inhibitors with other active drugs, there was higher risk of hypertension in case of active drugs.

The different effects of these different drugs reflect their different mechanisms of action, such as regulating blood pressure and modulating the immune system, as well as their potential for interacting with other drugs and their impact on comorbid conditions. Li et al. (2023) states the relationship between purines and purinoceptors blood pressure regulation to be intricate, making it a challenge to characterise the effect of the drugs upon hypertension. Thus, it I probable that the heterogeneous effects upon BP and hypertension associated with these inhibitors is the cumulative product of patient-specific factors, the drug's pharmacokinetics and the complex relationship immune modulation and cardiovascular physiology. To understand deeply the mechanisms that underpin these effects and to establish effective, safe protocols for using immunosuppressive drugs in those patients who are at risk of hypertension, more research is required.

8.5 Conclusion

In conclusion, the effects of these medications on hypertension were compared for our study and some previous studies concluded that there the medications under Purine and Pyrimidine synthesis inhibitors show different effects on the risk of hypertension. Some studies indicate that some medications increase and decrease the risk of hypertension. There were four studies which indicated that Mycophenolate Mofetil lead to a decrease the risk of hypertension. The studies related to Azathioprine showed no elevation in the risk of hypertension in their results. These results could not give a full explanation to the effects of these on Hypertension. However, most of the comparisons in the previous studies indicate that there was risk with Leflunomide only while others need re-investigation to understand the occurrence of hypertension can by using Purine and Pyrimidine synthesis inhibitors at standard doses.

8.6 Strengths and Limitations

Each considered study has both strengths and limitations which can affect the final outcomes directly or indirectly. Before we focus on the limitations, it is appropriate to highlight the strengths of our study. In the study there were some cases which were not able to give the complete justification to our hypothesis that the purines and pyrimidines can lessen the levels of blood pressure during the treatment of any inflammatory disorder. But the results of our own meta-analysis gave accurate and justifiable results. All these results concluded that these medications could reduce the risk of hypertension. There was some information that was collected from some unpublished data related to the studies. We took that data from the trials Sundel study which is concluded in this meta-analysis as well. These results were able to improve the quality of our study. Along with these strengths, our study also holds some limitations which of course added some negative impact to the results. There were main three limitations of our study. The first limitation that remained in the meta-analysis is that there are very rare studies that support our hypothesis. However, this is not limited to our study, as very few studies can provide a justification to the hypothesis. Along with rare results one more limitation we faced was that these justifications were not confirmed. Most of investigators have mentioned that these results need further investigation. None of them have mentioned the exact mechanism for these results. However, this investigation is rare and the outcomes of this meta-analysis will offer new and potentially beneficial information that can be used in future research. The second limitation of the study was too much data as our outcome hypertension is rare and which is usually reported as an adverse event, was not designed to be detected as a primary outcome in any of the included trials. Furthermore, there are no studies that support this hypothesis independently. Indeed, the sample size in most of the studies was small except Schiff, Emery and Vitko studies, which were slightly larger, but an extensive sample size is required to allow a more precise estimate of the treatment effect.Along with all these three main limitations there were some others but they did not cause any negative impact on the research. These include lack of time and insufficient information in

the study which required contacting the authors to obtain more details. Both strengths and limitations have influenced the outcomes of our study in some positive and negative manners respectively. Overall, the outcomes are logical and accurate to the best of our ability.

9. Association between Interleukin-1-beta Inhibitors and Risk of Hypertension

9.1 Introduction

Interleukin 1 beta (IL-1ß) is a pro-inflammatory cytokine that plays a key role in the body's immune response to infection and injury (Covello et al., 2009). Interleukin-1ß is one of 11 members of the interleukin-1 family. The interleukin-1 family has been researched extensively in a number of different studies, including *in-vitro*, preclinical, and clinical studies. In clinical studies, the blocking activity of IL-1 (mainly for IL-1ß) has since entered into the production of a range of clinical medicines (Dinarello, 2009).

There are a number of diseases associated with the Interleukin-beta-1, those being: systemic lupus erythematosus (SLE), osteoporosis and rheumatoid arthritis (Maruotti et al., 2014). Interleukin-1-beta (IL-1ß) inhibitors are drugs that block the action or production of IL-1ß, a pro-inflammatory cytokine that plays a key role in the body's immune response. Treatment with anakinra provides a cessation of the symptoms, Anakinra was the first selective IL-1Ra to have received approval from the US FDA in 2001. It was used for the treatment of rheumatoid arthritis and has proven itself to be efficacious in a broad spectrum of diseases (Dinarello et al., 2012).

Anakinra possesses a similar structure of human interleukin-1-receptor-antagonist (IL-1Ra). It is currently being used to treat a number of inflammatory disorders including rheumatoid arthritis (Mertens and Singh, 2009). The drug must be administered through a subcutaneous route even if it possesses a short half-life and poor bioavailability. The medication has been seen to reduce monocyte infiltrations, as well as inflammations in the synovial joints in case of rheumatoid arthritis (Fleischmann et al., 2004).

Canakinumab has a longer half-life of around 21-28 days. The drug was FDA approved in 2009 for the treatment of MWS (Muckle–Wells syndrome) and FCAS (familial cold auto-inflammatory syndrome). It was also approved of as a

treatment for CAPS by EMA (the European Medicines Agency)(Kuemmerle-Deschner and Haug, 2013).

Canakinumab has marginal effects on the levels of the lipids. Due to the prolonged effects of injection through subcutaneous routes, canakinumab is associated with minimal site reactions and can also cause a minor increase in the risk of infection (Ridker et al., 2011).Canakinumab is the third interleukin-1 blocker approved of for the treatment of autoimmune disorders, and is the second to approved for CAPS-treatment. Canakinumab binds to the human IL-1β with very high affinity (Dhimolea, 2010).

9.1.1 Mechanism of Action of Interleukin-beta-1 Inhibitors

There are 11 proteins (IL-1F1 through IL-1F11) in the interleukin-1 (IL-1) family of cytokines, which are produced by 11 different genes in mice and humans. IL-1-type cytokines play a significant role as primary regulators of innate immune responses. The use of interleukin-1 receptor antagonists (IL-1RA) to inhibit the activity of IL-1α and IL-1β, the Vital members of this cytokine family, has provided evidence for the central involvement of IL-1 in several autoinflammatory diseases affecting humans (Weber et al., 2010).

The roles of both intereukin-1-alpha and interleukin-1-beta in normal physiology and also in the pathophysiology of diseases is still unclear. This is due to the ubiquitous and non-specific nature of the production and effects of both IL-1-alpha and beta. The newly-produced IL-1Ra was found to be structurally similar to the IL-1-alpha and beta, and has been shown to bind to the receptors of various cells without inducing any biological response (Arend, 1991).

IL-1Ra is the first described naturally occurring antagonist of any cytokine. It is a member of the IL-1a family. There are two structural variants of IL-1Ra, those being sIL-1Ra and icIL-1Ra.The production of it by macrophages, monocytes, and neutrophils can be regulated in different fashions. The IL-1Ra bind to both IL-1RIs and IL-1RIIs on their surfaces (Arend, 1993).

A number of studies have shown that the Interleukin-1-beta is a good therapeutic target in various inflammatory disorders. These interventions directly target the interleukin-1 receptors, antagonising the receptor and the use of antibodies. Another approach is the use of inflammasome inhibitors. Anakinra binds directly to the receptor of interleukin-1. Canakinumab selectively binds to the receptor of interleukin. IL-1, a specific and a highly active proinflammatory cytokine central in inflammation which then drives the IL signalling pathway and contributes to tissue damage, then interacts with type-1 receptors (IL-1R1) and the adaptor protein IL-RAcP to enact signal transduction and activate NF-kB production. There are two main drugs depicted in **Figure 9-1** which can be used to limit the dependent hyper-inflammatory responses, those being anakinra (IL-1Ra) and canakinumab (Anti IL-1b)(Egan, 2021).

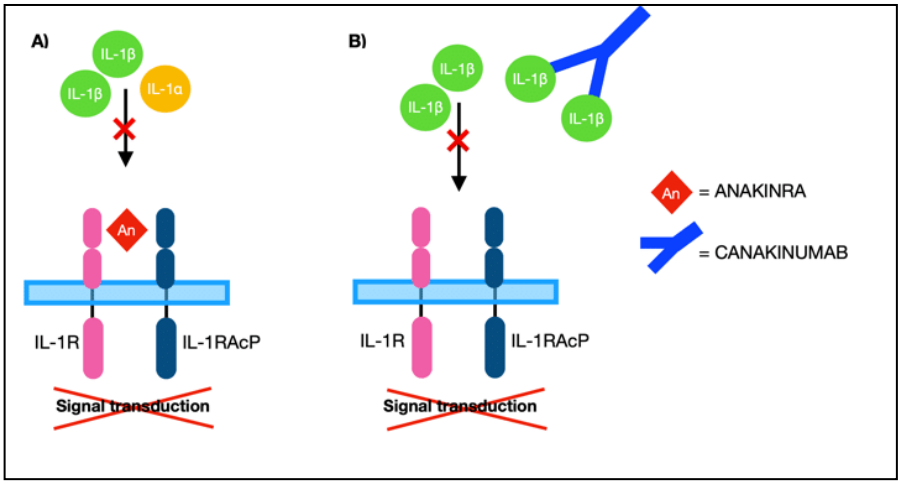

Figure 9-1 Scheme of the mechanism of action of anakinra and canakinumab.

Adapted from (Egan, 2021).

9.1.2 Hypothesis from Basic Science

In a number of previous research studies investigating the effects of interleukin-1-beta inhibitors on experimental animals (pre-clinical studies), certain justifications to our hypothesis regarding the meta-analysis may be found. As we seek to understand the effects of drugs in this class on hypertension risk, some

previous experimental preclinical studies may be examined that suggest different results.

In their paper, Ling et al. (2017) described the preclinical study of anakinra on male mice. The main focus of the study was on the activity of anakinra on various complications, such as renal dysfunction, damage to any tissue, and blood pressure. In this study, hypertension was induced by uninephroctomy and some other changes like feed. The systolic blood pressure was measured through the tail-cuff method. The intervention of this study found that anakinra had resulted in a reduction to blood pressure, and no hypertension-associated risk was found. The final results of the study indicated that the medication showed anti-hypertensive activity but also led to certain effects like inflammation and leukocyte infiltration. This study has suggested future investigation for these effects may be useful, but not for hypertension.

In another study produced by Zhang et al. (2016), researchers sought to investigate whether blocking the IL-1R1 receptor could protect against hypertension. For this investigation, researchers administered an IL-1R1 antagonist called anakinra alongside a placebo to WT mice for three days, both before and during chronic angiotensin-II infusion. It was found that anakinra treatment, much like IL-1R1 deficiency, did not affect baseline blood pressures when compared to the placebo. However, anakinra treatment significantly reduced the extent of blood pressure elevation during chronic angiotensin-II infusion, resulting in less cardiac hypertrophy following four weeks of hypertension. These results indicated that blocking the IL-1 receptor can cause a reduction to the risk of hypertension caused by angiotensin-II.

As both of these studies appear to indicate that the anti-interleukin-beta-1 receptor antagonist shows hypotensive activity, it can be concluded that these medications show anti-hypertensive activity in animals.

9.1.3 Rationale of the Study

There are some previous studies justifying our hypothesis that these medications can interfere with the risk of hypertension. These effects depend upon the dosage and efficacy of the medication itself.

A paper by Ikonomidis et al. (2008) studied an acute, double-blind trial involving 23 patients diagnosed with rheumatoid arthritis. The patients were treated with anakinra (subcutaneous injection) and a placebo. The assessment was conducted after 3 hours of injection. The final outcomes of the study indicated that the administration of anakinra had led to an increase in the aortic distensibility, whereby the strain was found to be higher. However, the main focus of our study is on hypertension. There were no significant changes uncovered on the levels of either systolic or diastolic blood pressure, whilst no significant differences were identified on a number of other cardiovascular parameters like heart rate, pulse, rate and the pulse.

In another study conducted by Van Beusecum et al. (2022), it was clearly indicated that patients with hypertension who had a systolic blood pressure of 130mm Hg or higher experienced a decrease in adverse reactions when treated with canakinumab. The medication also led to a decrease in the systolic blood pressure, which was less than 130mm Hg after treatment. The study also suggested a decrease of around 1.8% in the risk of hypertension and indicated that canakinumab can cause a reduction in the risk of hypertension.

Another case report by Schlesinger et al. (2012) investigated the effects of the same medication on patients with chronic tophaceous gout. The results of the study in phase III investigated the main adverse effects caused by this drug, including headaches, hypertension, and back pain. These results indicated that the drug canakinumab may be responsible in the elevation of blood pressure levels.

In another study conducted by Ebrahimi et al. (2018), a clinical trial was conducted in two centres in Switzerland. The trial involved 70 men with metabolic syndrome and low testosterone, who were randomly assigned to receive either a placebo or 200mg of anakinra twice a day for four weeks. Their other parameters related to metabolic syndrome were also investigated, like hyperglycemia, hypertension, and dyslipidemia. The majority at 71% were found to be suffering from hypertension. Adverse events were monitored throughout the treatment period and for two months afterwards, including fatigue, sexual dysfunction, and hypertension. The final results showed that anakinra treatment did not improve fatigue or sexual dysfunction, but that there had been a reduction in the mean arterial blood pressure. This result indicated the hypotensive activity of anakinra.

As such, in order to understand the effects of drugs in this class on the risk of hypertension, some previous experimental clinical studies may be consulted, many of which suggest different results. These are listed further in **Table 9-1.**

Table 9-1 Summary of key RCTs.

Study	Patients	Follow-up period	Intervention	Summary of results	References
Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure.	10,061	240 weeks	50,150,300 mg/kg canakinumab and a placebo.	Canakinumab did not have an impactful effect on hypertension and reduced the levels of blood pressure. The patients were likely to have hypertension and cardiac problems.	(Everett et al., 2019)
Arterial effects of canakinumab in patients with atherosclerosis and type 2 diabetes or glucose intolerance.	189	48 weeks.	Canakinumab 150 mg/kg was administered monthly for 12 months	As compared to the placebo drug canakinumab did not show any significant changes in blood pressure. There were also no significant differences between canakinumab comparing the primary efficacy and safety endpoints.	(Choudhury et al., 2016)

9.2 Methodology

9.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

9.2.2 Data extraction

The initial search yielded 95 articles using the search strategies detailed in the **Appendix A**, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of the research **(**see **Figure 9-2).**
After removing any duplications, the remaining 59 citations or abstracts were assessed for inclusion criteria. At that point, 43 articles were eliminated based on a title and abstract review process, almost 45% of the total, as predefined by the PICOS criterion. Of the 16 publications that remained for eligibility studies, 10 studies were eliminated after a full-text screening for several reasons which are described in **chapter 3,Table 3-1**. Ultimately, six trials with 2,496 patients were conducted for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

9.2.3 Description of excluded studies

A total of ten publications were excluded after an extensive eligibility check of their full texts. Five trials (Brucato, Fleischmann, Popovic, Tesser, and Asseldonk) reported different outcomes, though none mentioned hypertension (HTN). Two studies (Buckley and Wu) were removed for having a different display and different design.

Three studies (Krause, Schlesinger and Sunkureddi) were excluded because of their abstracts, participating in a conference without any details in the results. in **chapter 3,Table 3-1** summarises the reasons for the elimination of each trial.

9.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections.
Sensitivity analyses were completed by the exclusion of trials with [1] poor methodological qualities; [2] small sample sizes of less than 100 total participants.

Subgroup analyses for anti-IL1B were performed as follows: (1) clinical setting; (2) duration of follow-up.

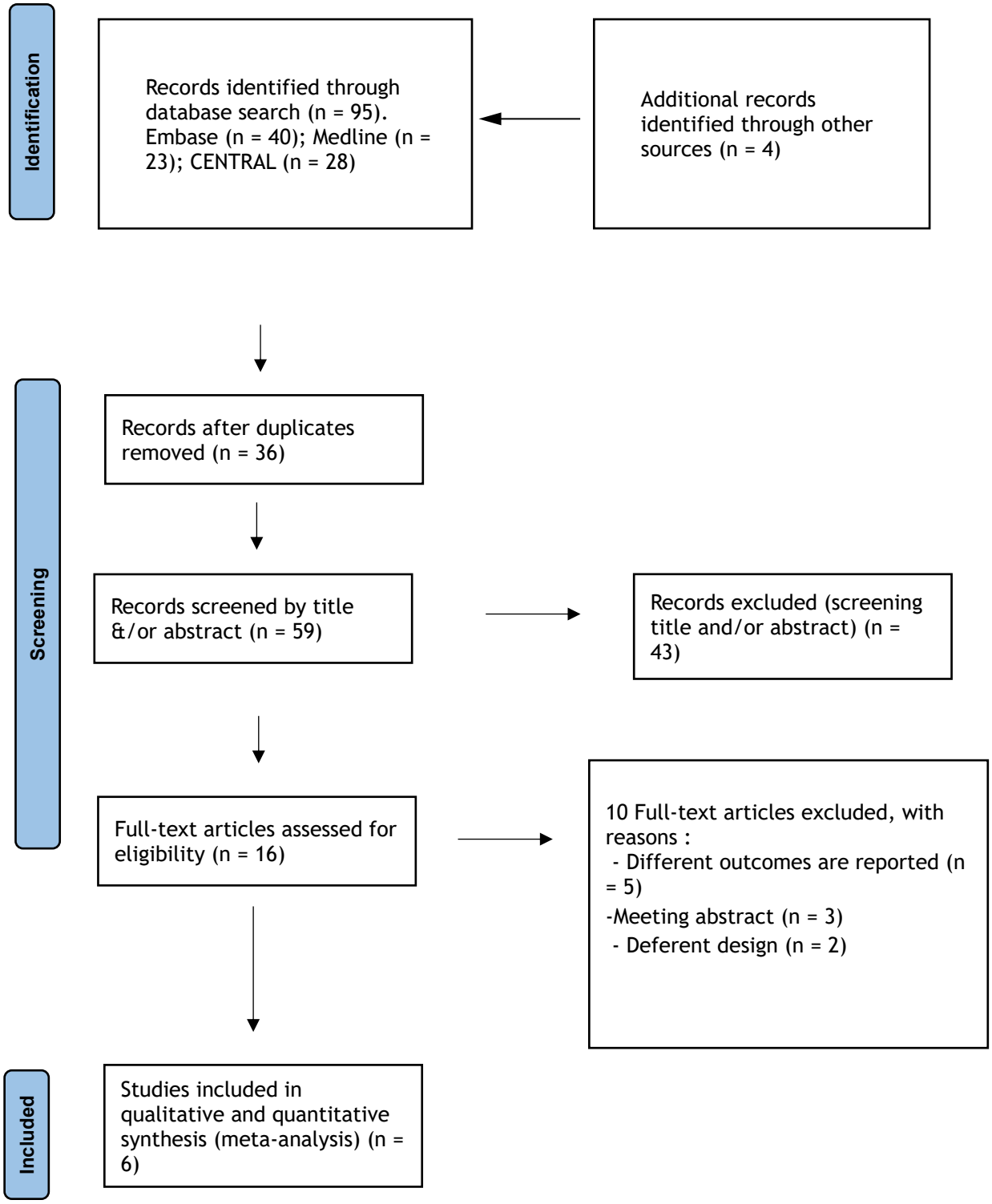

Figure 9-2 PRISMA Study flow diagram

9.3 Results

In total, 6 eligible Anti-IL-1β trials with 2,496 patients were conducted, with an average follow-up period of 1 year (ranging from three months to one year). The average patient age for all trials was 59 years old.
Figure 9-2 provides a summary of the trial searching and identification process. 10 studies were excluded for logical reasons. **Table 3-1 in chapter 3** records the reasons for the excluded studies and 6 RCTs (randomised controlled trials) were used for the final review.

The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**).

The majority of studies were published after 2004. One study published in 2011 is Alten's study, which investigated the effects of canakinumab in the treatment of rheumatoid arthritis and reported that a number of patients had experienced adverse effects, with one of those effects being hypertension. This study used canakinumab in different doses - 150mg, 300mg, and 600mg – as well as a placebo. One further study was that of Schiff, published in 2004 to investigate the effects of anakinra in the treatment of active rheumatoid arthritis patients. Another was Sheng (2020), which compared canakinumab at different doses (600mg and 300mg) with a placebo in patients suffering from Covid-19 and myocardial injuries.

All of the studies employed a double-blind design. None of the studies implemented a factorial design. The follow-up study periods were at least three months in length, with the longest being one year. All of the studies' participants were adults with a mean age of over fifty years old. Participants in the studies were both male and female, yet they differed in proportion from study to study. In this meta-analysis, we did not include subgroups of active drugs, as only one study compared our group with an active drug, and so it is impossible to include it in our meta-analysis.

Six studies were included in the meta-analysis that compared anti-IL1B to the placebo. A total of 1,834 and 662 patients were included in anti-IL 1B and the placebo groups, respectively, with an event rate of 0.92% and 1.8%. The risk of hypertension was not found to be significantly different between the groups (RR = 0.74, 95% 0.35; 1.6, P = 0.45), and no heterogeneity was observed between studies (I^2 = 0%, P = 0.87). The effect size was not statistically significant in any of the included studies. Ridher's study contributed to one-third of the meta-analysis weight, while other studies (Choudhury and Schiff) contributed to 29.8% and 11.5% (see **Figure 9-3**).

Similar results were obtained when a fixed-effects model was used (**Figure 9-4**). The difference in the risk of hypertension was not significantly significant between anti-IL1B and the placebo groups (RR = 0.81; 95% CI 0.39; 1.68, P = 0.56). Three of the six studies contributed to 80.6 % of the meta-analysis weight studies, those being Ridher, Schiff and Choudhury. No heterogeneity was observed between studies (I^2 = 0%, P = 0.87).

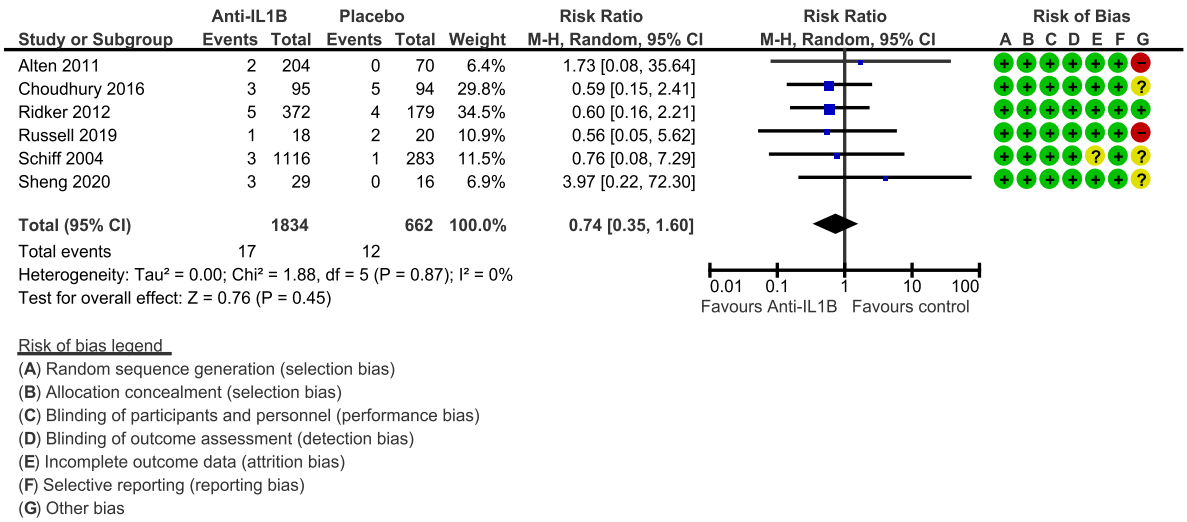

Figure 9-3 Random-effects model for the association between anti-IL1B and the risk of hypertension.

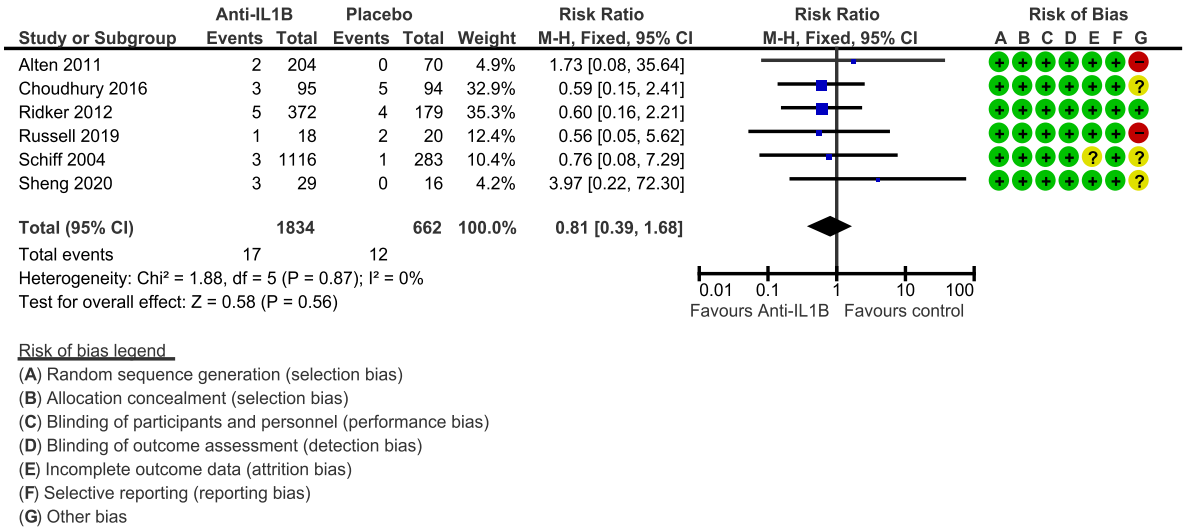

Figure 9-4 Fixed effects model for the association between anti-IL1B drug and the incidence of hypertension.

9.3.1 Sensitivity analyses

As **Figure 9-5** shows, the Alten trial was excluded from the meta-analysis due to high risk of bias. After this exclusion, the risk of hypertension was not found to be significantly different between anti-IL 1B and the placebo group (RR = 0.72, 95% CI 0.31; 1.68, P = 0.45). That analysis included 1,612 and 572 patients in the anti-IL 1B and placebo groups, respectively, and no heterogeneity was observed between studies (I^2 = 0%,P = 0.68).

The results of the original RE model meta-analysis did not change when three further studies (Choudhury, Russel, and Sheng) were excluded (RR = 0.72, 95% CI 0.25; 2.07, P = 0.54), indicating that the results are robust to the exclusion of studies with small sample sizes. That analysis included 1,692 and 532 patients in

the anti-IL1B and placebo groups, respectively, with no heterogeneity observed between studies (I^2 = 0%, P = 0.82)(see **Figure 9-6**).

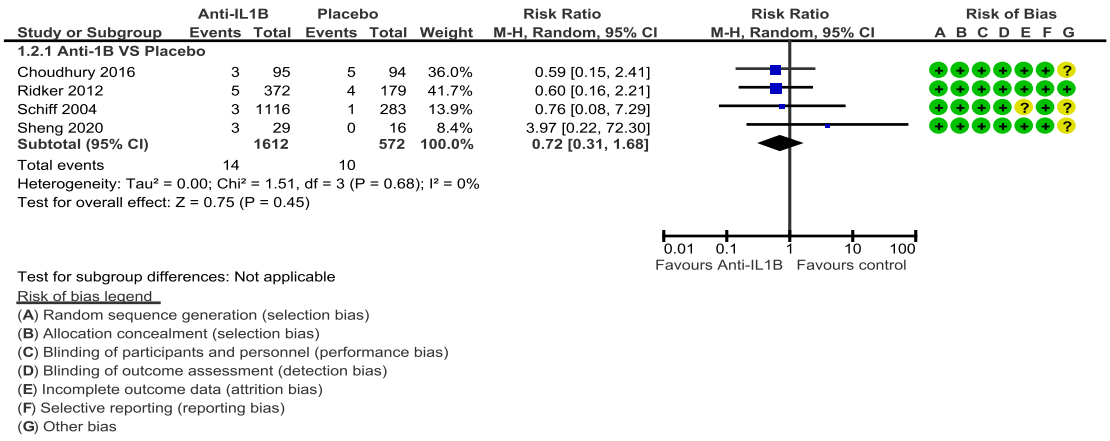

Figure 9-5 Sensitivity analysis for the association between the use of anti-IL1B and the risk of hypertension (RE model) after excluding studies with a high risk of bias .

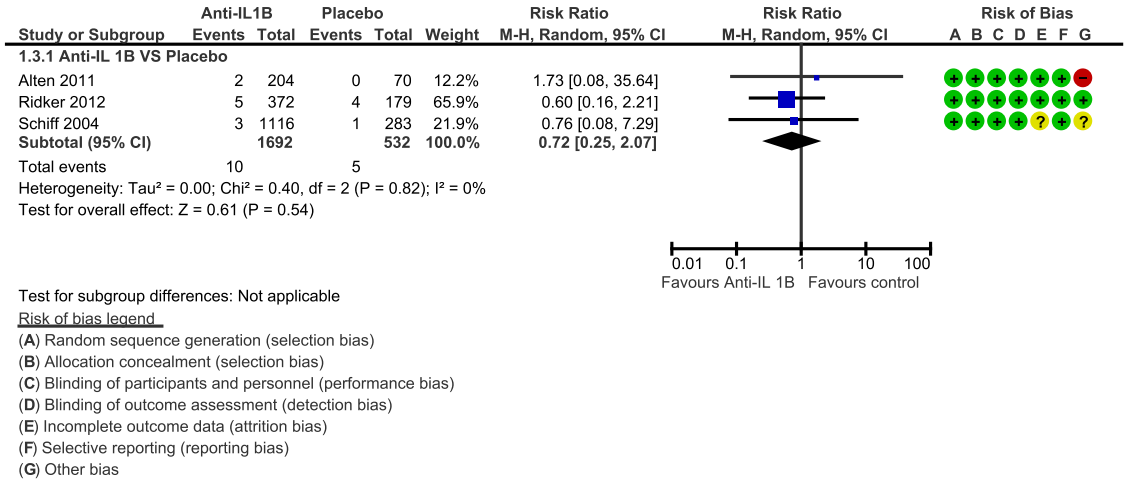

Figure 9-6 Sensitivity analysis for the association between the use of anti-IL1B and the risk of hypertension (RE model) after excluding studies with a low sample size.

9.3.2 Subgroup analyses

Table 9-2 summarises the subgroup analyses of anti-IL1B's impact on hypertension risks.

Only two studies included patients with HTN as a baseline **(Figure 9-10)**. The pooled estimate from the RE model was not statistically significant (RR = 1.00, 95% CI, 0.18; 5.41, P = 1.00), whilst low heterogeneity was observed between studies (I^2 = 27%,P = 0.24). The remaining four studies included patients with no HTN as a baseline. The pooled estimate revealed a risk ratio that was not statistically significant (RR = 0.69, 95% CI, 0.26; 1.80, P = 0.45). No heterogeneity was observed between studies (I^2 = 0%, P = 0.93)

The follow-up duration was under one year in four of the studies, and one year or more in the remaining two studies. When analysis was stratified by treatment duration, no association was observed between the use of anti-IL 1B and the risk of hypertension in patients followed up on for under one year (RR = 0.88, 95% CI 0.33; 2.38, P = 0.80) and those followed up on for one or more years (RR = 0.58, 95% CI 0.18; 1.94, P = 0.38). For the first subgroup, 1,721 and 548 patients were included in anti-IL 1B and control groups, respectively, with no heterogeneity observed between studies (I^2 = 0%, P = 0.65). For the second subgroup, 113 and 114 patients were included in the anti-IL 1B and control groups, respectively; however, in this case, no heterogeneity was observed between studies (I^2 = 0%,P = 0.96) (see **Figure 9-11**).

Table 9-2 The summary of a meta-analytical subgroup analysis by RE model demonstrating the effects of anti-interleukin 1 beta compared to a control (placebo and active) on the risk of hypertension.

Subgroup analysis		**Studies**		**Participant**	**event**	**Hypertension Incidence (%)**		**RR (M-H, Random, 95% CI)**	**P value***	**I^2 (%)**
						Anti-IL1B	Control			
Overall	RE	Placebo	6	2496	29	0.92	1.81	0.74 [0.35,1.60]	0.45	0
Clinical setting	Hypertension at baseline		2	234	11	4.8	4.54	1.00 [0.18,5.41]	1.00	27
	No hypertension at baseline		4	2262	18	0.64	1.26	0.69 [0.26,1.80]	0.45	0
Duration of follow-up	Less than two years		4	2269	18	0.75	0.91	0.88 [0.33,2.38]	0.80	0
	Two years or longer		2	227	11	3.53	6.14	0.58 [0.18,1.94]	0.38	0

† **List of definitions and abbreviations**: CI: confidence interval; RE: random-effects; RR: risk ratio; I2: I-square test for heterogeneity; M-H: Mantel-Haenszel; * If the P value is less than 0.05, it is considered statistically significant; ‡ I2 statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity;** Placebo and active drugs have been combined.

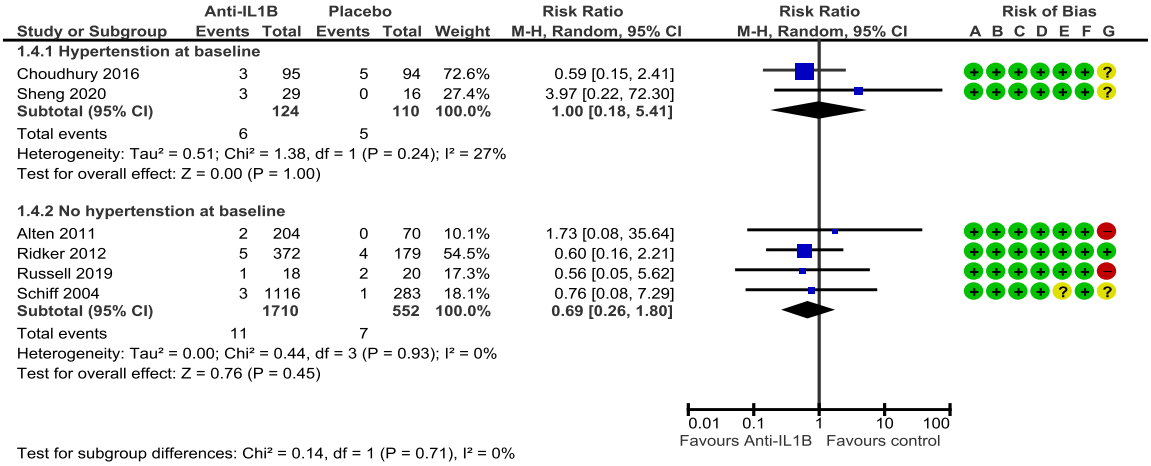

Figure 9-7 Subgroup analysis for the association between anti-IL1B and the risk of hypertension (the analysis was stratified by clinical population setting).

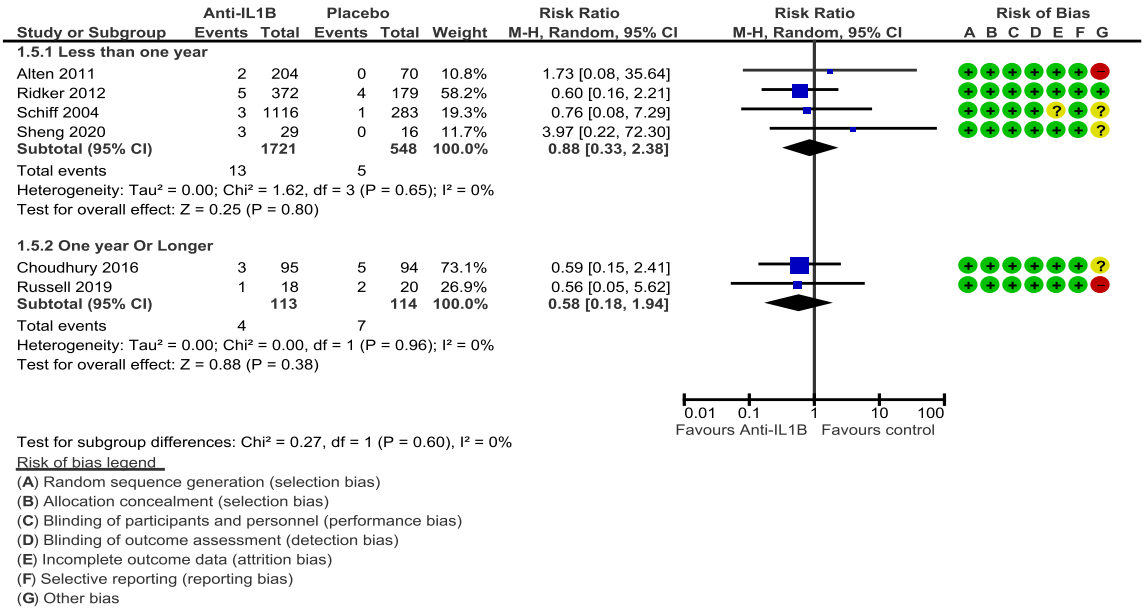

Figure 9-8 Subgroup analysis for the association between anti-IL1B and the risk of hypertension (the analysis was stratified by the duration of follow-up.).

9.4 Discussion

The final results of our meta-analysis on the basis of our hypothesis suggested that the interleukin-beta-1 – those being canakinumab and anakinra - did not cause any risk of hypertension.

Both anakinra and canakinumab are monoclonal antibodies which play a large role in the regulation of various types of immune responses. Interleukin-1-beta is a proinflammatory cytokine which plays a key role in inflammation. These are generally produced by immunocytes like macrophages and monocytes, which leads to inflammation. Interleukin-beta-1 has been seen to be involved in the development and progression of hypertension. Some studies have suggested that IL-1 beta plays a role in the regulation of blood pressure and the development of hypertension by promoting the production of other pro-inflammatory molecules, such as TNF-alpha and the activation of other immune cells.

A study conducted by Urwyler et al. (2020) investigated the effects of IL-1 antagonism (anakinra) on renin-angiotensin system peptide profiles and hemodynamic parameters in obese individuals over a short-term period of 2 days and a longer-term period of 4 weeks. The study consisted of two interventional trials. The results showed a significant reduction in the systolic blood pressure following both short-term and longer-term treatment with anakinra. No change in blood pressure was observed in the study in the placebo group.

In another study by Zhang et al. (2016), anakinra - an IL-1R1 receptor inhibitor - was found to significantly reduce blood pressure. This finding indicates that IL-1b may play a role in the development of hypertension.

In our study into the comprehensive meta-analysis findings of interleukin-1-beta's effects on the risk of hypertension, it can be suggested that there was no risk of hypertension with these medications when used to treat any inflammatory conditions.It can be indicated that these medications present a safe means of treating inflammatory disorders such as to eliminate the risk of hypertension which can be associated with said diseases.

From our comprehensive meta-analysis, it was shown that the risk ratio of hypertension was not statistically significant. In the comparison of interleukin1-

beta inhibitors against a placebo, no heterogeneity was observed and the results of this comparison were (RR = 0.74, 95% 0.35; 1.6, P = 0.45) and (I2 = 0%, P = 0.87).

However, a number of previous studies nevertheless exist which can support and provide justification to our hypothesis. The results of these vary with the type of study and also the dose received, alongside other factors that may be responsible for these variations, including the health status of the subject. Moreover, the final outcomes of the study can wane with time. The analysis mainly suggested that, when these monoclonal antibodies are compared to a placebo, they showed no significant differences. These results require re-investigation, with the includion of a number of factors for a clear and complete justification.

A study conducted by Rothman et al. (2020) indicated that interleukin-1-beta inhibitors can reduce the incidence of hypertension in patients with a residual inflammatory risk. However, both hypertension and inflammation are inter-linked physiologically, and whilst the effects of these specifically target the inflammation, their exact association is unknown. This has been mentioned in a recent study – the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) - which sought to test the mechanism of this result. Their analysis suggested that the mechanism may not be related to the incidence of hypertension.

Thus, from the whole research and analysis, we can conclude that medications classed as interleukin-1-beta inhibitors reduce the risk of hypertension when used to treat various inflammatory disorders. Some studies have also discussed how these two monoclonal antibodies have been used to treat diseases associated with hypertension when other biologics have not been able to treat it. It has been suggested that both these medications can be used to treat any inflammatory disorder associated with hypertension, as none of the previous studies have mentioned how both of these medications can increase the risk of hypertension.

As per previous studies, neither has been seen to cause no changes to the risk of hypertension, which clearly indicates that the sole effect of these medications on blood pressure is that they cause hypotension. From our study, only one result found no statistical differences between interleukin-beta-1 inhibitors and

placebos. In the information collected from all the previous studies, it was indicated that both of these monoclonal antibodies can be used to improve hypertension, whilst none have suggested that any further investigation is needed, suggesting that these medications have shown hypotensive activity in all cases. Whilst one case was presented in which the canakinumab was shown to cause a minor elevation in the levels of blood pressure, most of the studies have suggested that this drug decreases the risk of hypertension. As per our own research, however, as most of the studies show that this drug does not interfere with the risk of hypertension, we would like to suggest a further investigation of these results. Another justification of this unexpected result could be the existence of something common to those subjects preventing the results from being similar. By taking these factors into account, the study should be re-investigated. However, as a final result, it can be suggested that both of these medications do not cause any elevations in the risk of hypertension.

9.5 Conclusion

In summary, the findings of the meta-analysis showed that the use of anti-IL1B has no risk of hypertension when compared to placebo. Meanwhile, most of the previous studies indicated that there was no risk of incident hypertension. Therefore, the subject needs to be re-investigated to understand the occurrence of hypertension when interleukin-1-beta inhibitors are used at standard doses.

9.6 Strengths and Limitations

This study investigated the body of comprehensive analysis that exists into the association of hypertension risk with inhibitors of interleukin-1-beta and found some results that seem to justify our hypothesis; and yet, our study still holds some limitations. However, alongside these limitations, much like every study ours also boasts a number of strengths as well. As such, before we discuss the limitations of our study, we would first like to highlight the strengths of our study. Both limitations and strengths have affected our study in direct and indirect ways.

Some information was collected from certain unpublished datasets related to the studies. We took that data from the trials of Sheng, Choudhury, Alten and Russell, which was concluded in this meta-analysis as well. These results were able to improve the quality of our study. Along with these strengths, our study also holds some limitations which has naturally negatively impacted upon our results. One limitation of our research is that most of the previous studies have suggested future justifications and, due to the lack of a full explanation, we could not have a complete and full justification to the hypothesis, even if most of the previous studies have justified theirs. Another limitation that our study holds is that, even if most studies have supported our hypothesis, none of them have discussed the exact mechanism for these results. However, this investigation is rare - the outcomes of this meta-analysis offer new and potentially beneficial information that can be used in the future. A third limitation of this study was that too much study as our outcome hypertension is rare and which is usually reported as an adverse event, was not designed to be detected as a primary outcome in any of the included trials and there are no studies that support this hypothesis independently. The sample size in most of the studies was small, except for the study of Schiff , which were slightly larger. An extensive sample size is required to allow for a more precise estimate of the treatment effect.

All of these limitations have collectively led to some lack of complete information to our study. Along with all of these three main limitations, there were some others that did not cause any negative impacts upon our research. These included a lack of time and insufficient information, required that we contact the authors of certain studies to obtain more details. Both strengths and limitations have influenced the outcomes of our study, though the overall results are considered logical and accurate.

10. Association between Colchicine and the Risk of Hypertension

10.1 Introduction

Colchicine is a tricyclic alkaloid that causes an interruption in some multiple inflammatory response pathways. This tricyclic alkaloid can be extracted from two plants, Meadow Saffron (also known as Autumn Crocus) and Glory Lily; the scientific names of these plants are *Colchicum autumnale* and *Gloriosa superba*, respectively (Yang, 2010). Colchicine is used to treat gout, a well-known auto-inflammatory disorder that is a type of arthritis triggered by the crystallisation of uric acid in the joints. Gout is associated with impaired metabolism of purines (hyperuricemia) which causes joint pain and chronic tophaceous gout develops after years. Gout is associated with other abnormalities like hypertension, neuropathy and insulin resistance disease (Choi et al., 2005).

In 2009, the United States Food and Drug Administration (USFDA) approved an oral formulation of colchicine named Colcrys to treat Gout flares and its prophylaxis. Currently, it is the only single colchicine agent with FDA approval (Sundy, 2010). although some other colchicine formulations approved by the FDA use it in combination with probenecid or other NSAIDs including sulindac, naproxen and indomethacin. All these combinations are approved by the USFDA to treat acute gout flares but none of them is approved for gout prophylaxis (Yang, 2010). The medication is also approved in the USA for certain other conditions in addition to gout; colchicine can be used for several other disorders including cirrhosis, psoriasis , necrotising vasculitis, Behcet's syndrome, Sweet's syndrome, systemic sclerosis, sarcoidosis, amyloidosis and in the prophylaxis of familial Mediterranean Fever (Ben-Chetrit and Levy, 1998).

Colchicine was isolated by Caventou and Pelletier in 1820 and its original structure was elucidated by Windaus in 1924. In 1945, Dewar proposed a formula where colchicine contains a tropolone ring system, which is now accepted and has also received a justification (Hartung, 1954) .

10.1.1 Mechanism of Action of Colchicine

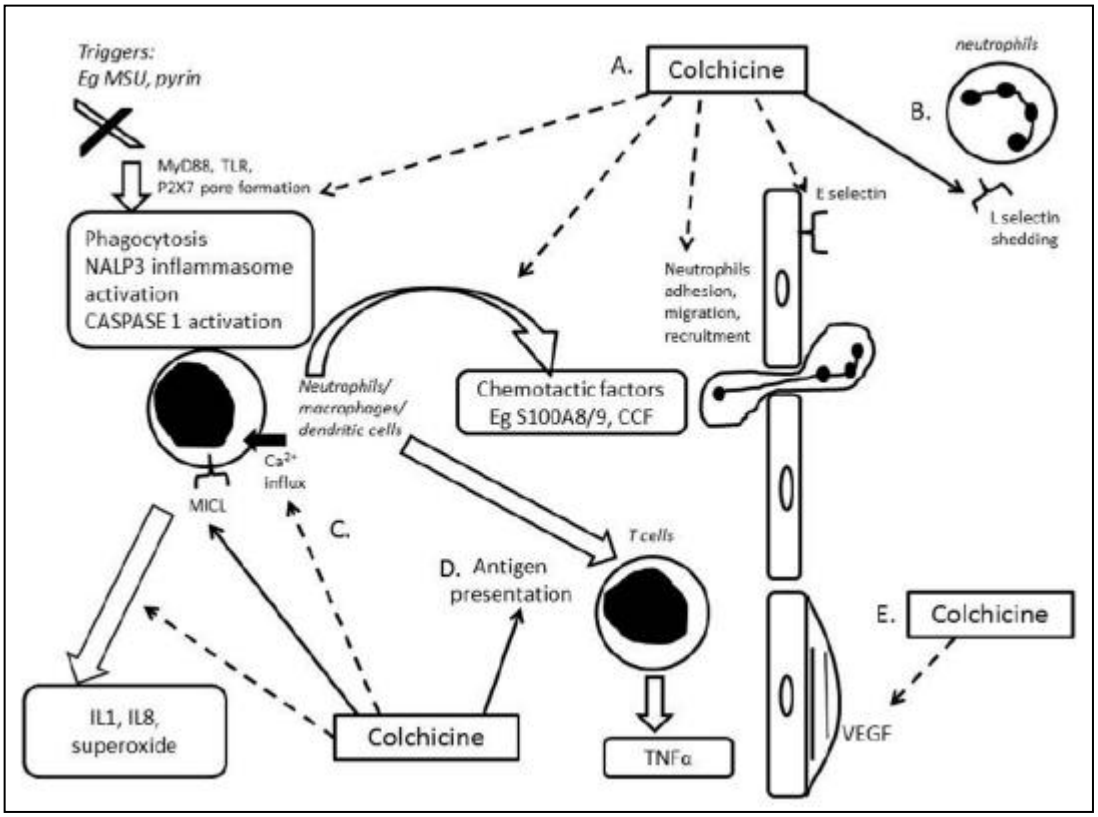

Figure 10-1 Anti-inflammatory Mechanism of Colchicine

Adapted from **(Leung et al., 2015)**

Colchicine has several mechanisms of action that promote its anti-inflammatory activity, as depicted in **Figure 10-1.** These include inhibition of innate immunity activation, inhibition of inflammasome activation, and caspase-1 activation. These collectively inhibit the release of chemotactic factors from neutrophils. In low concentrations, colchicine causes the inhibition of the expression of E-selectin on endothelium and leads to neutrophil adhesion. At high concentrations, it promotes the L-selectin shedding from neutrophils. Colchicine also inhibits the activation and release of IL-1, IL-8 and Superoxide-D. Colchicine promotes the maturation of dendritic cells to act as antigen-presenting cells, also inhibiting

vascular endothelial growth factor (VEGF) and the proliferation of endothelium. The anti-inflammatory properties of colchicine are mostly associated with microtubule disruption and leucocytes' downstream cellular functions. Colchicine's most studied therapeutic mechanism of action is that it binds to tubulin, thus blocking the assembly and polymerisation of microtubules. As the key components of the cytoskeleton, microtubules are made up of α and ß-tubulin heterodimers. Microtubules play a role in cellular functions including cell shape preservation, intracellular trafficking, cytokine and chemokine secretion, cell migration, cell division and ion channel modulation. As a traditional anti-mitotic medication, colchicine prevents mitotic cells from dividing during metaphase (Leung et al., 2015).

10.1.2 Hypothesis from Basic Science:

Several previous studies on colchicine have been conducted on experimental animals (pre-clinical studies), which may provide some justification of the present paper's hypothesis and meta-analysis. To understand the effects of colchicine on the risk of hypertension, some previous studies suggest different results, as detailed below in **Table 10-1**.

Table 10-1 Selected previous preclinical studies

Study	Design of study	Animal used	Results/Summary	References
Effect of Colchicine on urinary phosphate and regulation by parathyroid hormone	Lab test	Sprague-Dawley Albino Rats	Colchicine did not show any alterations to blood pressure levels and other parameters like inulin clearance and fractional clearance of K and Na^+ levels.	((Dousa et al., 1976)
Microtubules are involved in early hypertrophic responses of the myocardium during pressure overload	Lab test	Rats	The study suggested that *in-vivo* administration of colchicine did not cause any weight loss and there was an elevation in systolic arterial blood pressure in both rats with colchicine than those operated with sham. Also, there were no significant differences in systolic arterial pressure in both groups.	(Takahashi et al., 1998)
Colchicine Improves Survival, Left Ventricular Remodeling, and Chronic Cardiac Function After Acute Myocardial Infarction	Lab test	Mice (Male)	There were no significant changes in systolic blood pressure and heart rate between both vehicle and colchicine groups.	(Fujisue et al., 2017)

10.2 Methodology

10.2.1 Search strategy and eligibility criteria

Comprehensive descriptions of the methods used for this systematic review and meta-analysis were described in **Chapter 2 (Methodology for all groups).**

10.2.2 Data extraction

The initial search yielded 36 articles using the search strategies detailed in the Appendix A, obtaining information from bibliographic and non-bibliographic database sources. The PRISMA study flow diagram summarises the identification of the research **(**see **Figure 10-2).**After removing duplicates, the researchers assessed the remaining 33 citations or abstracts for inclusion criteria. At that point, eight articles were eliminated based on a title and abstract review process, almost 25% of the total, as predefined by the PICOS criterion. Of the 25 publications that remained for eligibility studies, 21 studies were eliminated after a full-text screening for several reasons, which are described in **chapter 3,Table 3-1**. Ultimately, four trials with 899 patients enrolled for the qualitative and quantitative synthesis of this final review. The excluded and included studies have been described in the methodology sections.

10.2.3 Description of excluded studies

This paper excluded a total of 21 publications after an extensive eligibility check of their full text. Of the 21 excluded studies, 1 trials reported different outcomes, which did not mention hypertension (HTN); two studies (AGREE and Krishnan) were removed for having a different design; five studies (Bardin, Becker, Brucato, Leung and Schlesinger) were excluded because the abstracts outlined participation in a conference without any details in the results; one study was a review. in **chapter 3,Table 3-1** summarises the reasons for elimination for each piece.

10.2.4 Meta-analysis

The statistical analysis methods used in this study were described in Methodology sections. There were too few studies to perform sensitivity and subgroup analyses.

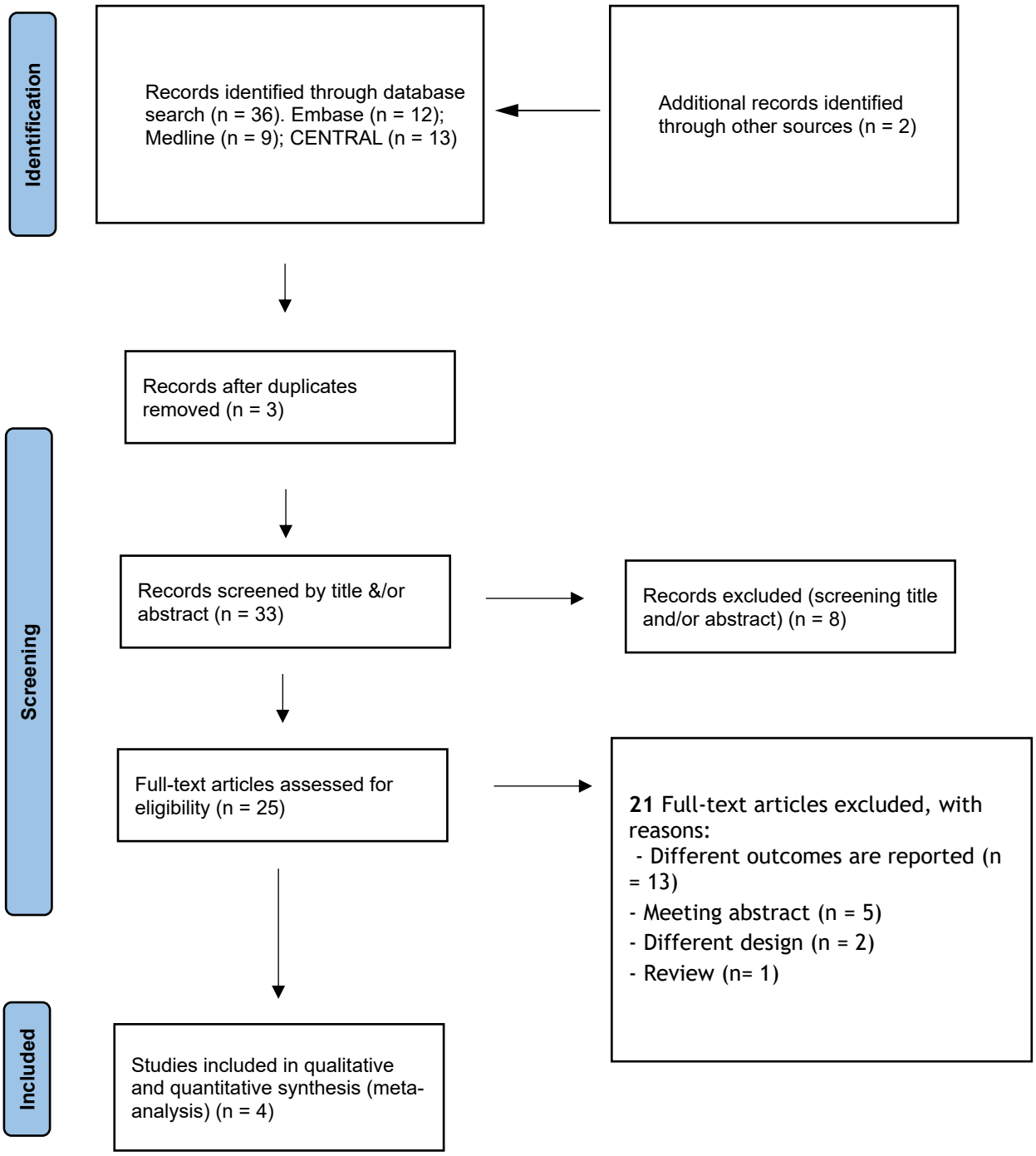

Figure 10-2 PRISMA Study flow diagram

10.3 Results

In total, four eligible colchicine trials with 899 patients were enrolled, with an average follow-up period of one year (ranging from three months to one year). Meanwhile, the average patient age for all trials was 47 years old. **Figure 10-2** provides a summary of the trial search and identification process.
Twenty-one studies were excluded for logical reasons. **Table 3-1 in chapter 3** records the reasons why these studies were excluded. The fundamental characteristics and bias risk of the studies included in this review have been described previously (See **Chapter 3, section 3.2.2 and Appendix C**). This paper used four randomised controlled trials (RCTs) in the final review as only these four included a meta-analysis for both subgroups.

The Poiley study (2016) divided 248 patients with gout into three different groups; the first group was a placebo group; the second group was given arhalofenate with different doses (600mg and 800mg); the third group was treated with colchicine plus allopurinol 300mg. The Poiley study reported many incidents of hypertension.

The Terkeltaub study (2010) compared different doses of colchicine (1.8mg and 4.8mg) to a placebo in patients with acute gout flare. The Schlesinger study (2011) divided 432 patients with gouty arthritis into multi arms of canakinumab with different doses (25mg, 50mg, 100mg, 200mg and 300mg) compared to colchicine in 0.5mg doses. The Pakfetrat study (2010) compared colchicine to prednisolone in patients with aphthous stomatitis.

All these studies reported the incidence of hypertension and other conditions. The four studies employed a double-blind design, and none implemented a factorial design. The follow-up study periods were at least three months and the most extended was one year. All the study participants were adults with a mean age of over forty years old. All participants in the studies were male and female but differ in proportion from study to study.

As mentioned above, only four studies were identified that assessed the risk of hypertension in colchicine and were thus included in the meta-analysis (see **Figure 10-3**). Two studies compared colchicine to a placebo and three compared it to other active drugs. The risk of hypertension was not significantly different between colchicine and the placebo (RR = 0.50, 95% CI 0.10; 2.38, P = 0.38) and the present study did not observe any heterogeneity between studies (I^2 = 0%, P = 0.96). Only three events occurred in each group. When colchicine was compared to other active drugs, the present study did not observe any statistically significant differences in the risk of hypertension between groups (RR = 0.44, 95% CI 0.09; 2.11, P = 0.31). Low heterogeneity was observed between studies (I^2 = 35%, P = 0.21). Only three events occurred in patients who received colchicine (1.7%) compared to 25 cases in patients who received other active drugs (5.5%), which suggests that colchicine carries a lower risk of hypertension.

Fixed-effects meta-analysis also showed that the risk of hypertension was not significantly different between groups (RR = 0.50, 95% CI 0.10; 2.37, P = 0.38). However, the risk of hypertension was significantly lower in colchicine than in other active drugs (RR = 0.33, 95% CI 0.11; 1.05, P = 0.06), while the difference was statistically significant at the 0.05 level (see **Figure 10-4**).

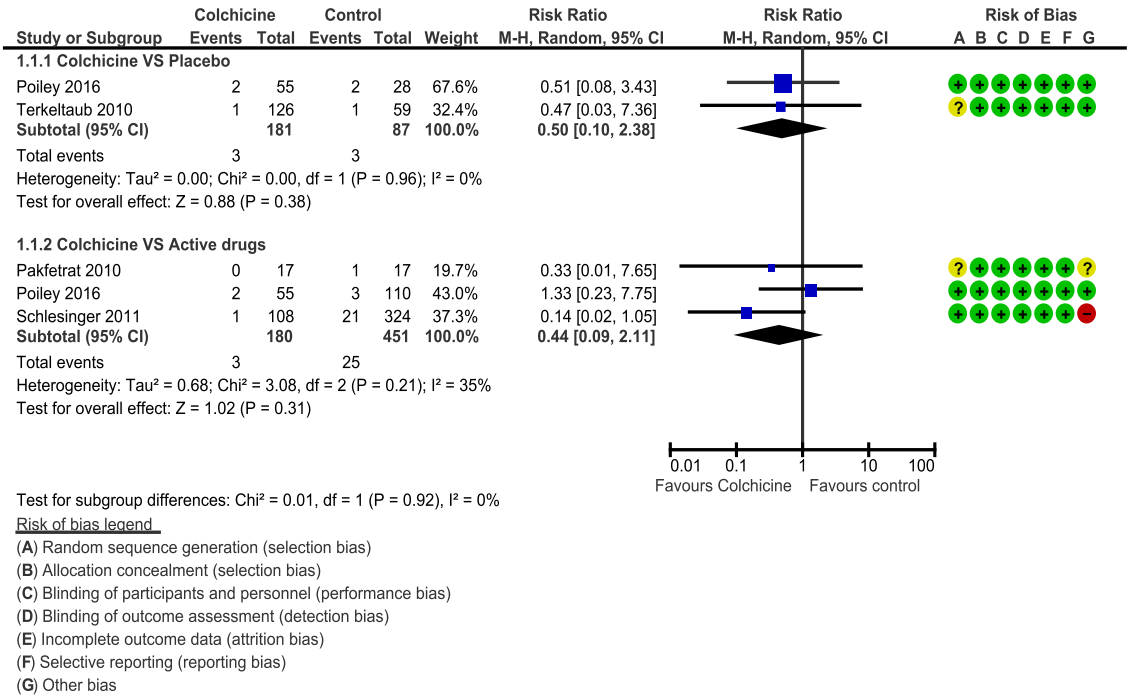

Figure 10-3 Random-effects model for the association between Colchicine and the risk of hypertension

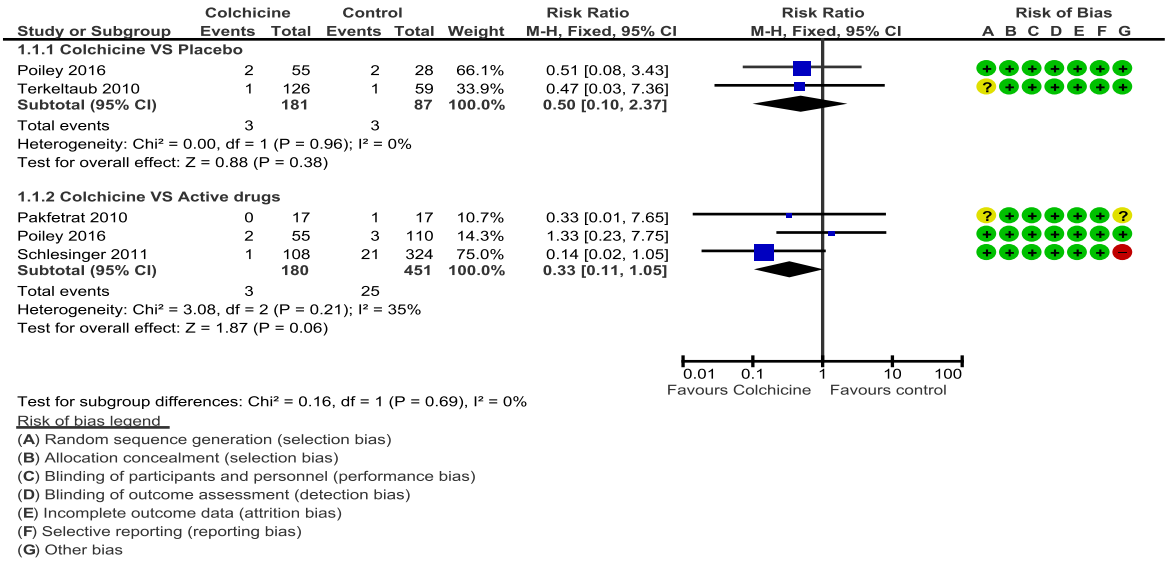

Figure 10-4 Fixed-effects model for the association between Colchicine and the risk of hypertension.

10.4 Discussion

The final results of this meta-analysis based on our hypothesis suggested that colchicine did not cause any risk of hypertension when compared to both placebo and other drugs.

This meta-analysis identified that the risk of hypertension was not significantly different between placebo and colchicine. The results of this comparison were (RR = 0.50, 95% CI 0.10; 2.38, P = 0.38). When a comparison was made between colchicine and other active drugs, there was no significant difference and no risk of hypertension was observed between these two groups. The results of this comparison were (RR = 0.44, 95% CI 0.09; 2.11, P = 0.31).

Numerous studies have researched the effects of colchicine upon BP. For example, Solomon et al. (2016) conducted a cohort study, in which electronic medical records linked to Medicare claims were analysed. The researchers concluded that among gout patients, colchicine might ameliorate cardiovascular disease. However, Zhang et al. (2022) argues that the majority of studies have failed to identify a significant beneficial effect of colchicine upon BP. One study hypothesises that ß-adrenoceptor-mediated vasodilation could be promoted by colchicine; this might be helpful in treating essential hypertension (Ehlers et al., 2022). In contrast, other studies have found colchicine does not have a significant anti-hypertensive effect (Lagrue et al., 1985, Shen et al., 2022). These conflicting findings of about colchicine's effect upon BP and the risk of hypertension could be accounted for by variations in the study's populations, including the presence of comorbidities, and the dosage and duration of colchicine treatment administered.

Guan et al. (2013) study investigated the effects of colchicine on hypertensive chronic kidney disease and identifies hypertension as a risk factor for this disorder. Guan et al. state that when associated with impaired renal auto-regulation, hypertension can increase intra-glomerular pressure (Pgc). The final outcomes of the study suggest that colchicine can modify hypertensive renal fibrosis, while the authors suggest that a new potential for the usage of this medication could be the prevention of hypertension in cases of kidney-related fibrosis, also indicate that colchicine did not cause any effect on systemic hypertension. Finally, the study suggests that evaluating colchicine in combination with other medications that can increase blood pressure levels is of significant interest and could provide a greater clinical benefit.

Zhang et al. (2022) study summarises the current clinical trials concerning the curative effects of colchicine for various cardiovascular diseases, as well as discussing its mechanism as a cardiovascular therapeutic. Zhang et al. found no changes in the lipid profile in the blood and colchicine also had no effect on blood pressure; however, there were some improvements in microcirculatory parameters and a reduction in atherosclerosis. The authors suggest that since colchicine possesses anti-inflammatory activity, it provides a naturally occurring and promising cardiovascular medication, and its efficacy makes it a good athero-inflammatory agent.

Keeley and Alatawi (1991) study looked at aortic elastin synthesis responses and the development of hypertension. The authors also investigated the inhibitory actions of colchicine and suggest that hypertension establishment occurs due to the increase in the connective tissue protein on the walls of large arterial blood vessels, used the Dahl salt-sensitive rat model for systemic hypertension and also used a renal clip. In hypertension models, an increase in accumulated arterial elastin appeared with an increase in blood pressure; when colchicine treatment was given, this marginally affected the rise in blood pressure but also abolished the response.

However, some previous studies conducted on the effects of colchicine on blood pressure levels can support and provide justification for our hypothesis. The results of studies on the effects of colchicine can vary and the factors that cause these variations include the type of study, the dose received and the state of the patient for example, the disease they are suffering from. It is also possible that the final outcomes of some studies may wane with time. The analysis from the previous study suggested that colchicine does not cause any changes in blood pressure levels, while Keeley and Alatawi (1991) study found it causes only marginal effects on the rise of blood pressure. These studies clearly indicate that colchicine has no or very little effect on blood pressure. The results of these studies need further investigation and during the re-investigations, several factors should be taken into account for comprehensive and fair justification.

10.5 Conclusion

In conclusion, all the studies investigated in this paper except one suggest that the medication colchicine does not cause any changes in blood pressure levels, meaning that there is no associated risk of hypertension. It is important to note that the use of colchicine is primarily intended for the treatment of gout and other inflammatory conditions and any potential risks or benefits related to hypertension should be carefully considered in the context of a patient's overall health status and treatment plan. The association between colchicine use and the risk of hypertension is a complex and multifaceted issue that requires further research and investigation. More research is needed not only to fully understand the relationship between colchicine and hypertension but also to identify any potential mechanisms or factors that may contribute to this association. Ultimately, the decision to prescribe colchicine should be based on a thorough evaluation of a patient's individual health status and risk factors, as well as a

careful consideration of the potential benefits and risks associated with the medication.

The present study found a lack of previous clinical studies because most RCTs did not show any results related to hypertension. This is why so few studies were included in the meta-analysis. However, this paper's meta-analysis reviewed two comparisons: the first between colchicine and placebo groups and the second between colchicine and other active drug groups. Both comparisons indicated that colchicine has no associated risk of hypertension.

10.6 Strengths and Limitations

The research conducted on the comprehensive analysis of hypertension risk and its association with colchicine found some results that can provide justifications for our hypothesis, but there are also some limitations. Like every study, this paper also has strengths in addition to limitations. In terms of strengths, some information was collected from unpublished data related to the studies. this data from trials conducted by Terkeltaub included this in the meta-analysis. These results improved the quality of this study. Another strength of the study was that all the previous studies identified have shown similar results except one. All the previous studies except one suggested that colchicine does not cause any changes in blood pressure levels, meaning that there is no associated risk of hypertension. The only study that stated no changes at all was Keeley and Alatawi (1991) research, which claimed that colchicine causes marginal effects on increasing blood pressure; however, such marginal effects may not increase the risk of hypertension. In the comparison done for meta-analysis, there was no indication of a risk of hypertension.

The results of the majority of previous studies and our meta-analysis found similar results, thus justifying our hypothesis. Along with these strengths, this meta-analysis also holds some limitations, the main one being the lack of clinical studies; since most of the randomised control trials did not have any data related to hypertension, very few studies could be included in the meta-analysis. However, although these investigations are rare, the outcomes of our meta-analysis offer new and potentially beneficial information that can be used in future.

11.General discussion and prospects

11.1 General Overview

This chapter provides an encapsulation of the principal outcomes of this research endeavour. It contextualizes the findings within the larger scientific discourse by comparing them to similar studies while also delineating the strengths and limitations inherent in the research design. Furthermore, it elucidates the study's implications for clinical practices and future research initiatives. At its core, this research constitutes an exhaustive review to delineate the impact of diverse immunosuppressive therapy classes on hypertension risk in patients contending with various autoimmune diseases. To this end, a meta-analytical approach was implemented, enabling the research to synthesize vast quantities of data to draw more definitive conclusions. This facilitated a deeper understanding of the intricate relationship between immunosuppressive therapies and hypertension risk, paving the way for enhanced patient management and informed healthcare strategies.

11.1.1 Summary of the Main Results

In the comprehensive review conducted for this study, 141 trials involving 60,580 participants were evaluated. The aim was to assess the impact of selected immunosuppressive therapies on the risk of hypertension. These therapies included methotrexate (MTX), TNF inhibitors (anti-TNF), interleukin 6 inhibitors (anti-IL6), interleukin 17 inhibitors (anti-IL17), interleukin 1B inhibitors (anti-1B) , purine and pyrimidine inhibitors (including leflunomide, mycophenolate, and azathioprine), and colchicine.

The analysis of methotrexate (MTX) indicated no significant difference in the risk of hypertension when compared to a placebo (RR = 0.93, 95% CI, 0.61; 1.44, P = 0.75). However, when compared with other active drugs, a statistically significant reduction in hypertension risk was noted, favouring the MTX drug (RR = 0.47, 95% CI, 0.34; 0.65, P = 0.00001). The findings concerning methotrexate demonstrated potential benefits when compared with alternative anti-inflammatory treatments, including a decreased risk of hypertension.

In the case of anti-IL6 inhibitors, there was no significant difference in the hypertension risk when compared to a placebo or other active drugs (RR = 1.2, 95% CI 0.82; 1.73, P = 0.35) and (RR = 1.48, 95% CI 0.97; 2.25, P = 0.07). Similarly, anti-IL17 inhibitors displayed no significant effect on the risk of hypertension, when compared to a placebo (RR = 1.09, 95% CI 0.75, 1.58, P = 0.65) or other active drugs (RR = 0.89, 95% CI 0.60, 1.31, P = 0.54).

The results for anti-TNF inhibitors were significantly different. The risk of hypertension was elevated for participants on anti-TNF inhibitors than for those given a placebo (RR = 1.31, 95% CI 1; 1.73, P = 0.05) but, statistically, at the edge of significant risk. However, when compared with other active drugs, the hypertension risk did not significantly differ (RR = 1.14, 95% CI 0.73; 1.78, P = 0.56).

The analysis of purine and pyrimidine inhibitors revealed that the risk of hypertension was slightly elevated than the placebo but not statistically significant (RR = 1.37, 95% CI 0.78; 2.44, P = 0.28). Notably, a significantly lower hypertension risk was observed when compared to other active drugs, favouring purine and pyrimidine inhibitors (RR = 0.81, 95% CI 0.65; 0.99, P = 0.04).

For anti-1B inhibitors, there was no significant difference in hypertension risk compared to other groups (RR = 0.74, 95% 0.35; 1.6, P = 0.45). When considering colchicine, there was no significant difference in the risk of hypertension, whether compared to a placebo (RR = 0.50, 95% CI 0.10; 2.38, P = 0.38) or other active drugs (RR = 0.44, 95% CI 0.09; 2.11, P = 0.31).

In the realm of immunosuppressive therapies, a substantial body of research has predominantly focused on individuals without pre-existing hypertension. This is a crucial point of consideration when attempting to extrapolate the results of these studies to the treatment of hypertension directly. Hypertension, characterized by chronically elevated blood pressure, entails a complex interplay of various pathophysiological mechanisms, including but not limited to, dysregulated renin-angiotensin-aldosterone system, endothelial dysfunction, increased sympathetic nervous activity, and altered vascular structure and function. Immunosuppressive

therapies, which work primarily by dampening the immune system's response, may have differential effects on hypertensive individuals due to their unique pathophysiological landscape.

These results present a view of how different classes of immunosuppressive therapies might impact the risk of hypertension. They demonstrate that methotrexate, purine, and pyrimidine inhibitors might be associated with a reduced risk of hypertension when compared to other drugs, whereas anti-TNF inhibitors have the potential to increase this risk, which was on the borderline of significant. Anti-IL6, anti-IL17, anti-1B inhibitors, and colchicine do not significantly affect the risk. These findings clarify the complex interplay between immunosuppressive therapies and hypertension risk and have the potential to allow for increasingly informed decisions in clinical practice. The **table 11-1** provides a summary of the results for each agent, comparing them to a placebo or other active drugs.

Table 11-1 Summary of results:

Agents	Type of control	Hypertension Risk (RR)	95 % CI	P-value
Methotrexate	Placebo	0.93	0.61;1.44	0.75
	Active drugs	0.47	0.34;0.65	0.00001
Anti-TNF	Placebo	1.31	1;1.73	0.05
	Active drugs	1.14	0.73;1.78	0.56
Anti-IL17	Placebo	1.09	0.75;1.58	0.65
	Active drugs	0.89	0.60;1.31	0.54
Anti-IL6	Placebo	1.2	0.82;1.73	0.35
	Active drugs	1.48	0.97;2.25	0.07
Purine,Pyrimidine inhibitors	Placebo	1.37	0.78;2.44	0.28
	Active drugs	0.81	0.65;0.99	0.04
Anti-IL1B	Placebo	0.74	0.35;1.6	0.45
Colchicine	Placebo	0.50	0.10;2.38	0.38
	Active drugs	0.44	0.09;2.11	0.31

11.1.2 Research Strengths

The most prominent strengths of this work are discussed in the results section of each individual chapter. For a majority of studies included in this review, the methodological quality is high. As far as the researcher is aware, the review is the largest and most comprehensive systematic review and meta-analysis of RCTs that has ever been conducted. Moreover, this study may offer significant new information regarding how exposure to the main types of immunosuppressive medications affects hypertension risk in a target group. The extensive search approach enabled me to gather the most pertinent citations and publications. The primary strength of the current review was the use of a thorough search strategy employing bibliographic databases, as well as additional non-bibliographic database sources such as the ClinicalTrials.gov website. By using these search techniques, I was able to include further articles and unpublished data.

Secondly, the strict inclusion criteria ensured that sample sizes were sufficient to provide results for different interventions that are noticeably different. In a population with various health settings, stratified analyses were also carried out concurrently to evaluate potential confounding by indication. This is essential in obtaining accurate measurements of how immunosuppressive medications affect medical outcomes (such as the risk of hypertension).

11.1.3 Research Limitations

To be more precise, the limitations have been discussed and analysed in each chapter. On the whole, the most significant limitation of the current meta-analyses is that it was performed using aggregate data, which can induce ecological bias in the findings. When the average score for a patient's features fails to accurately reflect the true impact of individual-level properties, this causes a bias. Since the average doses between trials would be more or less equal, there would be little opportunity to differentiate between the trials, even if the doses of immunosuppressive medications may have affected the research results.

Thus, to overcome these constraints, patient data can be pooled. A sensitivity analysis that excluded high-risk trials was carried out. Another potential limitation of this work is that there may be clinical heterogeneity among the recruited people with hypertension, diabetes, CVDs, or other illnesses. Although the studies included in this review examined the impacts of various subgroup populations on pooled effect size certain subgroups had insufficient power, which could have limited the conclusions that were drawn. Moreover, most of the effect estimates were homogeneous (evidenced by the I^2 value of 0%) and only a small number of outcomes were linked to an I^2 value of >50%, supporting the validity of the results. Moreover, another significant obstacle encountered in this study was that all cases of hypertension were found to be unfavourable effects rather than main outcomes. Additionally, the bulk of population samples were small, making a larger sample size more accurate and reflective of the population as a whole.

11.1.4 Comparison with Other Reviews

This study, drawing from human clinical studies, investigates the potential risk of hypertension associated with several immunosuppressive therapies. The treatments under review include methotrexate, Anti-TNF agents, Interleukin 6 inhibitors, Interleukin 17 inhibitors, Interleukin 1B inhibitors, purine, and pyrimidine inhibitors, and colchicine. This research specifically selected studies conducted on humans and excluded animal studies. To conduct this analysis, indirect comparisons were utilised to infer relationships between treatments based on separate trials that share a common treatment. The strength and validity of the meta-analyses rely on the quality and similarity of the included trials. This process identified 141 review studies including designs and outcomes. This comprehensive analysis and treatment comparison is essential for healthcare professionals to make informed decisions regarding treatment options while considering the compromises between risks and benefits. The network meta-analysis is grounded in a systematic review which adheres to the PRISMA Extended Statement to ensure a robust investigation. The adherence to rigorous

methodologies enables this study to provide a reliable evaluation of the relationship between immunosuppressive therapies and the risks of hypertension. Multiple mechanisms influence the effects of different immunosuppressive agents upon BP. To illustrate, azathioprine and methotrexate both inhibit cell division in rapidly proliferating cells, which might have an effect upon BP regulation (Scherer et al., 2023). A putative relationship has been proposed between inhibiting TNF and regulating BP, as agents that target TNF have been associated with an elevated risk of developing hypertension (Zhao et al., 2015). Also, interleukins have been linked to the pathophysiology of hypertension; a clear association has been revealed in studies in which IL-6 infusions caused a dose-dependent vasopressor response, resulting in elevated blood pressure (Tanase et al., 2019). These various findings indicate that the mechanisms by which immunosuppressive agents act on BP might arise from their effects upon proinflammatory cytokines, vasoactive substances, and by modifying the immune system. Consequently, to make informed drug-prescription decisions for patients at risk of hypertension, it is important to develop a deep understanding of the mechanisms used by these agents to modulate BP.

Numerous studies have explored the influence of Methotrexate (MTX) on hypertension risk when treating autoimmune conditions. The first study to assess the impact of Methotrexate in treating several autoimmune conditions on the hypertension risk network was conducted by Atkinson et al. (1988) whose systematic analysis revealed that patients receiving cyclosporin exhibited an enhanced rate of marrow engraftment. However, they also experienced higher incidences of oropharyngeal mucositis, azotemia, and diastolic hypertension than individuals treated with Methotrexate. The actuarial four-year survival rates for recipients of MTX were 69% while CSP recipients had a survival rate of 43%, however, this difference did not reach statistical significance. Additionally, an examination of the survival rates, specifically those for continuous complete remission from the time of transplant, was revealed to be 69% for MTX recipients and 38% for CSP recipients, and these differences were also not statistically significant ($p = 0.09$). The study found that cyclosporin resulted in enhanced

marrow engraftment but was associated with more mucositis, azotemia, and diastolic hypertension than Methotrexate.

A study conducted by Ikonomidis et al. (2019) involved 120 patients who were randomly assigned to receive anakinra (an IL-1 inhibitor), tocilizumab (an IL-6 inhibitor), or prednisolone (a corticosteroid) for three months. Regardless of the treatment group, all patients exhibited improvements in left ventricular longitudinal strain, coronary flow reserve, malondialdehyde (an oxidative stress marker), protein carbonyls (another oxidative stress marker), and C-reactive protein levels following the treatment period (when compared to the baseline). Notably, anakinra treatment resulted in greater improvements in longitudinal strain (18.7%) and coronary flow reserve (29%) compared to tocilizumab (9.7% and 13%) and prednisolone (6% and 1%), respectively. Tocilizumab treatment also demonstrated benefits in reducing arterial stiffness and brachial blood pressure when compared to the baseline. Based on these results, it can be inferred that the risk of hypertension with Anti-IL6 therapy does not statistically deviate from that linked to other medications.

Kircik et al. (2016) conducted a comprehensive analysis by amalgamating data from four, separate, phase 3 trials to scrutinize the effectiveness of Secukinumab (Interleukin 17 inhibitor) in treating moderate-to-severe psoriasis, specifically in the head and neck region, by employing the HNPASI score as a tool to measure the level of improvement in patients. The results of their study highlighted the rapid improvement observed in patients following treatment with Secukinumab: significant reductions in HNPASI scores became evident as early as the first week and these improvements remained consistent throughout the year-long study. The consistency of Secukinumab's efficacy and safety were verified across all four trials. Furthermore, while the study did report instances of hypertension as an adverse event, it was deemed manageable given the low discontinuation rate due to adverse events. Thus, the study concluded that the overall safety profile of Secukinumab was satisfactory, implying that any occurrences of hypertension were effectively controlled.

Davis et al. (2021) adopted a different approach by taking a broader view, examining the role of Interleukin 17A (IL-17A) in the genesis of hypertension and its potential as a therapeutic target. Rather than focusing solely on the effects of Anti-IL17 on hypertension, it explored the wider correlation between IL-17A and hypertension. The paper collated findings from multiple studies, including those conducted by Davis et al., highlighting the relationship between IL-17A levels and hypertension. For example, diabetic patients suffering from hypertension were found to have significantly elevated plasma IL-17A levels compared to those without hypertension. Additionally, a correlation was found between circulating IL-17A levels and systolic blood pressure in pre-hypertensive individuals.

While Kircik et al. (2016) and Davis et al. (2021) offer valuable insights concerning the role of IL-17A and the impact of its inhibition in different health contexts, it is evident that IL-17A could be involved in the pathogenesis of hypertension. Kircik et al. (2016) demonstrated that Secukinumab (an Anti-Interleukin 17) has a substantial therapeutic effect in the treatment of psoriasis, with hypertension noted as a potential adverse event. Conversely, Davis et al. (2021) reinforced the potential link between IL-17A and hypertension, suggesting that anti-IL-17 treatment might influence hypertension.

Zhao et al. (2015) explored the connection between anti-TNF treatments for rheumatoid arthritis (RA) and hypertension which aimed to evaluate the risk and prevalence of hypertension induced by anti-TNF therapy in RA patients. This rigorous analysis pooled data from eleven clinical trials and encapsulated a substantial patient pool of 6,321 which enabled the researchers to determine that the pooled incidence of hypertension related to anti-TNF therapy was 3.25%. They concluded that the use of anti-TNF agents was linked to a considerable increase in hypertension risk (when compared to controls) and that the risk appeared to escalate throughout the treatment.

In contrast, Sandoo et al. (2011) conducted a longitudinal study to understand the impact of anti-TNF therapy on blood pressure and vascular function in RA patients. They assessed blood pressure, microvascular, and macrovascular functions and observed a significant reduction in systolic and diastolic blood pressure among

subjects undergoing anti-TNF therapy over twelve weeks. The study attributed this reduction to the enhanced endothelium-dependent microvascular function prompted by the therapy. Notably, no such changes in blood pressure were detected in the control group. The study concluded that anti-TNF therapy could cause a reduction in blood pressure in RA patients, potentially mediated by improvements in microvascular function.

Faria et al. (2021) explored the effects of Anti-TNF therapy on resistant hypertension (RH) via a randomised, double-blind, placebo-controlled pilot trial where RH patients were administered either a one-time dose of infliximab or a placebo. Unlike the placebo, infliximab treatment notably decreased mean and diastolic blood pressure levels. This significant difference in blood pressure levels (post-infliximab infusion) indicates the drug's potential effectiveness in managing resistant hypertension, suggesting an encouraging new paradigm for treatment. Zhao et al. (2015) associate anti-TNF therapy with an increased risk of hypertension among RA patients while Sandoo et al. (2011) and Faria et al. (2021) observed blood pressure reductions post-treatment, suggesting the potential of hypertension management via anti-TNF therapy.Cao et al. (2019) executed a meta-analysis exploring the effects of mycophenolate mofetil (MMF) on blood pressure by merging data from various studies. This analysis led to a significant finding: MMF therapy slightly reduced diastolic blood pressure (DBP) but left systolic blood pressure (SBP) unaffected which indicates that MMF therapy might moderately lower DBP without modifying SBP, potentially reducing hypertension-related cardiovascular risks. Contrastingly, Hollander et al. (1995) conducted a single-centre study investigating the outcomes of shifting from cyclosporin to azathioprine therapy post-kidney transplantation. They understood that cyclosporin therapy was linked to hypertension suggesting a potential role in higher cardiovascular mortality. Conversion to azathioprine led to less frequent hypertension which highlights the benefits of this therapeutic shift in blood pressure management. The meta-analysis conducted by Cao et al. (2019) suggests modest DBP reduction with MMF treatment while Hollander et al. (1995) provide evidence that a therapeutic conversion to azathioprine might reduce the occurrence of hypertension. Such discoveries improve the understanding of how

certain post-transplantation medications might influence blood pressure management in hypertensive patients.

Rothman et al. (2020) assessed the effects of IL-1B inhibition with canakinumab on blood pressure and the onset of hypertension. The results demonstrated a non-significant change in the risk of hypertension between the treatment groups with a relative risk (RR) of 0.74 (95% CI: 0.35 to 1.6, P-value: 0.45), suggesting that anti-IL-1B treatment does not markedly alter hypertension risk. Conversely, Everett et al. (2020) examined the impact of anti-inflammatory therapy with canakinumab on cardiovascular events in high-risk patients. The results revealed a significant decrease in serious cardiovascular events, with rate ratios (RRs) of 0.80 (50 mg), 0.79 (150 mg), and 0.78 (300 mg) when compared to a placebo.

Reviews conducted by Rothman et al. (2020) and Everett et al. (2020) reveal the complex effects of anti-IL-1B treatment on cardiovascular outcomes. Rothman et al. (2020) observed no significant effect on hypertension although it is important to note that hypertension represents only one component of cardiovascular risk. Conversely, Everett et al. (2020) highlighted a significant reduction in serious cardiovascular events which suggests that IL-1B inhibition benefits extend beyond blood pressure control. Despite their different outcomes, Rothman et al. (2020) focused on hypertension, and Everett et al. (2020) on a broader spectrum of cardiovascular events, offering important insights into anti-IL-1B treatment.

Rahimi et al. (2020) conducted a retrospective cross-sectional study, involving twenty-one patients who suffered from colchicine poisoning, which measured various clinical features and outcomes and correlations with survival were established. Based on their results, there was a significant correlation between lower blood pressure (systolic and diastolic) and survival rates in patients with colchicine poisoning. The p-values for systolic and diastolic blood pressure were 0.010 and 0.002, respectively and these low p-values indicate that the results are statistically significant and cannot be solely attributed to chance. The lower blood pressure in this context could be a result of the body's response to colchicine poisoning or a side effect of the poisoning itself. In support, Bruns (1968) presented a case study of a single patient experiencing colchicine toxicity in which

they demonstrated transitory hypertension, preceding the onset of convulsions, nine days after ingesting colchicine. The blood pressure subsequently normalized. Both studies noted changes in blood pressure associated with colchicine toxicity but the nature of these changes differed. In the first study, lower blood pressure was associated with survival while the second study observed transient hypertension before convulsions. Both studies suggest that colchicine toxicity impacts blood pressure although the observed effects differ which could be due to individual variations in response to colchicine poisoning, the severity of the poisoning, or other factors that were not taken into consideration. In our study, it is important to address the exclusion of corticosteroids from our analysis, based on a clear justification stemming from the well-established association between corticosteroid use and hypertension, which is extensively documented in medical textbooks and research studies. Because of their impact on endothelial dysfunction, the renin-angiotensin-aldosterone system, and changes in vascular structure and function, corticosteroids have been shown to raise the risk of hypertension.

11.2 Research Implications

This review highlighted a significant gap in research evidence comparing selective immunosuppressive therapies with placebo or anti-inflammatory medications and their impacts on the risk of hypertension.

Although data are available for the 60,580 participants in this review. In this review, aggregate data from varied studies were employed and pooled. Nonetheless, estimates may be skewed as a result of differences in the distribution of trial- or patient-level features between studies, which ultimately impacts the relative efficacy of the interventions under comparison. In addition, most large-scale trials enrolled individuals who had previously used or were now on DMARDs, biological agents, or anti-inflammatory medications; this may have attenuated the genuine effect estimate.

The same methodology is employed in individual participant data (IPD) meta-analyses and traditional systematic reviews/meta-analyses. Furthermore, most

researchers prefer this approach as it can enhance the quality of the data obtained and subsequent analysis. In turn, this renders the findings more reliable. Nonetheless, to ensure that this method is successful, researchers must work closely together. This ensures the validity of trial data and ultimately minimizes the chances for reporting bias to occur.

11.3 Implications for Clinical Practice

The findings from this thesis offer an in-depth comparative analysis of the efficacy of various medications on hypertension risk and found significant differences in the risk profiles of these medication groups. Methotrexate, purine, and pyrimidine inhibitors (including leflunomide, mycophenolate, and azathioprine) demonstrated a potential for hypertension protection while other medication groups, such as colchicine, anti-interleukin 6 , anti-interleukin 1B and interleukin 17 inhibitors, had no significant effect on hypertension risk. These results lead the way for a more evidence-based selection of medication groups for hypertension management, emphasising the need to weigh the potential benefits against the risks in a patient-specific context.

The results of this study may provide a level of reassurance for clinicians and patients alike. Certain medication groups, specifically colchicine and anti-interleukin-6 , anti-interleukin-1B and interleukin-17 inhibitors, did not increase hypertension risk which may be especially significant in multi-morbid patients, where an exacerbation of hypertension could complicate their overall health status. Therefore, these medications might be deemed to be moderately safer for such patients, provided other potential side effects and contraindications are considered. Additionally, the data contained in this study revealed that methotrexate, purine, and pyrimidine inhibitors demonstrate a protective effect against hypertension when compared to anti-inflammatory treatments. These findings highlight these groups as potentially superior options for managing hypertension, especially in high-risk patients; however, this must be balanced against potential side effects and individual patient tolerance.

This research emphasises the importance of individualising therapy for hypertension. While methotrexate, purine, and pyrimidine inhibitors exhibited protective effects against hypertension, anti-TNF inhibitors displayed borderline statistical significance while other medications showed no significant effect. These variances highlight the necessity for a personalised, patient-centred approach which considers factors such as the patient's overall health status, potential risk factors, and the specific hypertension profile. While these findings provide a deeper understanding of the impact of various medication groups and their impact on hypertension, the absence of adequate head-to-head trials limits the robustness of these results. It is strongly recommended that future research conducts such trials to allow for a more direct comparison of the relative effects of these medications which will enable the creation of definitive guidance for clinical practices.The availability of generic versions of methotrexate and purine and pyrimidine inhibitors means that these groups have become cost-effective options for managing hypertension. However, decisions regarding their prescription should not be made purely on an economic basis but should consider the overall benefits to the patient, tolerance levels, and potential side effects.

11.4 Future Works

In presenting the associations between different immunosuppressive agents and the risk of hypertension, this thesis’s findings can be used a springboard for various avenues of future research. Therefore, these findings need to be disseminated to the target audience of healthcare professionals and the scientific community through a reputable, peer-reviewed journal. To achieve that publication goal, the research findings need to be prepared, a suitable journal needs to be identified and the submission guidelines followed. Then it is hoped that the manuscript will be peer reviewed and reviewer feedback provided, so the manuscript can be refined and finalised for publication. The published work will provide interested parties with current evidence that can be used to inform clinical decisions relating to immunosuppressive therapies and hypertension. I intend to conduct further research in rheumatology and organ transplantation clinics across Saudi Arabia. The collection and analysis of data from patients prescribed these

immunosuppressants will provide a deeper understanding of the practical implications of these drugs on blood pressure in real-world scenarios. Direct patient-level data will enable the authors to account for various patient characteristics, including age, gender, comorbid conditions, lifestyle factors, and concomitant medications, which can influence the observed effects. Another direction for future research involves conducting longitudinal studies on these patients which involves the monitoring of changes in blood pressure over time and assessing the long-term effects of these medications on hypertension risk , Such studies can provide valuable insights into the safety and tolerability of these drugs on a long-term basis. Future research could extend to these patient populations to understand if the observed effects also apply to them. Additionally, to explore the underlying mechanisms that might explain the varied effects of these drugs on hypertension risk. Understanding the biological basis for these effects can provide more nuanced guidance for clinical decisions and may indicate potential strategies for mitigating hypertension risk. In addition to the clinical effects, there would be interest in conducting a pharmacoeconomic analysis involving a study of the cost-effectiveness of these drugs, considering their impact on hypertension and the potential savings which would arise from avoiding hypertension-related complications.

11.5 Conclusion

In summary, this study used data from 60,580 participants. The results suggest that the overall risk of hypertension associated with each of the seven groups of drugs differs. Anti-Interlukin-6 agents, anti-Interlukin-17, interleukin-1beta, colchicine appear not to affect the risk of the occurrence of hypertension (when compared to a placebo or other active drugs). Methotrexate and purine and pyrimidine synthesis inhibitors, in turn, appear to reduce the risk of high blood pressure in comparison to other anti-inflammatory treatments. Anti-TNFs agents are linked to a borderline risk of developing hypertension when compared to placebos. The groups also differ in their heterogeneity with some having extremely low heterogeneity while others have significant internal differences; nevertheless, most are highly homogeneous with the results of similar studies being almost identical.

Appendices

Appendix A: Electronic database search strategies

MP in the title, original title, abstract, topic header, and registry word fields denotes multipurpose search keywords;"tw" denotes that the term is a text word with a meaning, title, and abstract; "Pt." denotes several types of publications, including reviews, clinical trials, directories, and letters; "ab" denotes every word that can be searched from the abstract; “/” indicates that it is a Medical Subject Heading (MeSH) term; “$” indicates all possible suffix variations of the root words; "?" denotes the retrieval of documents that use British or American word variations;“adj” plus a number between any two terms returns records that contain both terms, within the specified number of words from each other.

IMP inhibitors		
MEDLINE (OVID)	**Cochrane**	**EMBASE (OVID)**
1. IMP Dehydrogenase/ 2. (azathioprine or leflunomide or mycophenolate mofetil).tw. 3. 1 OR 2 4. hypertension/ 5. hypertens$.tw. 6. (blood adj pressure).tw. **7. 4 or 5 or 6** 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. Randomized.ab. 11. Placebo.tw. 12. Drug therapy.tw. 13. Randomly.ab. 14. Trial.ab. **15. 8 or 9 or 10 or 11 or 12 or 13 or 14** 16. animals/ not (humans/ and animals/) **17. 15 not 16** **18. 3 and 7** 19. **17 and 18**	1. MeSH descriptor: [IMP Dehydrogenase] explode all trees 2. (azathioprine OR leflunomide OR mycophenolate):ti,ab,kw **3. #1 OR #2** 4. Hypertension.mp. 5. Hypertens$.tw. **6.** (blood adj pressure).tw. **7. #4 OR #5 OR #6** 8. **#3 and #7**	1. IMP Dehydrogenase/ 2. (azathioprine or leflunomide or mycophenolate mofetil).tw. **3. 1 OR 2** 4. hypertension/ 5. hypertens$.tw. 6. (blood adj pressure).tw. **7. 4 or 5 or 6** 8. randomized controlled trial/ 9. Crossover procedure/ 10. Double-blind procedure/ 11. (randomi$ or randomly).tw. 12. (crossover$ or cross-over$).tw. 13. Placebo$.tw. 14. (doubl$ adj blind$).tw. 15. Assign$.ab. 16. Allocat$.ab. 17. Trial.ti. **18. 8 or 9 or 10 or 11 or 12 or 13**

		19. **or 14 or 15 or 16 or 17** 20. (animal$ not (human$ and animal$)).tw. **21. 18 not 19** **22. 3 and 7** 23. **20 and 21**
TNF inhibitors		
MEDLINE OVID	**Cochrane**	**EMBASE (OVID)**
1. exp Tumor Necrosis Factor Inhibitors/ 2. (TNF adj2 (inhibit$ or blockade?)).tw. 3. Anti-TNF agent$.tw. 4. (infliximab or etanercept or golimumab or certolizumab or adalimumab).tw. **5. 1 or 2 or 3 or 4** 6. hypertension/ 7. hypertens$.tw. 8. (blood adj pressure).tw. **9. 6 or 7 or 8** 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. Randomized.ab. 13. Placebo.tw. 14. Drug therapy.tw. 15. Randomly.ab. 16. Trial.ab. **17. 10 or 11 or 12 or 13 or 14 or 15 or 16** 18. animals/ not (humans/ and animals/) **19. 17 not 18** **20. 5 and 9** 21. **19 and 20**	1. MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees 2. TNF near/2 (inhibit* or blockade*).ti,ab,kw 3. (anti-tumor necrosis factor?):ti,ab,kw 4. TNF near/4 receptor next (inhibit* or blocker*):ti,ab,kw 5. (anti-TNF agent*):ti,ab,kw 6. (infliximab OR etanercept OR golimumab OR certolizumab pegol OR adalimumab):ti,ab,kw **7. #1 OR #2 OR #3 OR #4 OR #5 OR #6** 8. Hypertension.mp. 9. Hypertens$.tw. **10.** (blood adj pressure).tw. **11. #8 OR #9 OR #10** 12. **#7 AND #11**	1. Exp Tumor Necrosis Factor Inhibitors/ 2. (TNF adj2 (inhibit$ or blockade?)).tw. 3. Anti-TNF agent$.tw. **4.** (infliximab or etanercept or golimumab or certolizumab pegol or adalimumab).tw. **5. 1 or 2 or 3 or 4** 6. hypertension/ 7. hypertens$.tw. 8. (blood adj pressure).tw. **9. 6 or 7 or 8** 10. randomized controlled trial/ 11. Crossover procedure/ 12. Double-blind procedure/ 13. (randomi$ or randomly).tw. 14. (crossover$ or cross-over$).tw. 15. Placebo$.tw. 16. (doubl$ adj blind$).tw. 17. Assign$.ab. 18. Allocat$.ab. 19. Trial.ti. **20. 10 or 11 or 12 or 13 or 14 or 15or 16 or 17 or 18 or 19** 21. (animal$ not (human$ and animal$)).tw.

		22. 20 not 21 **23. 5 and 9** 24. **22 and 23**
Interleukin 6 (Anti-IL-6)		
MEDLINE (OVID)	**Cohrane**	**EMBASE (OVID)**
1. (interleukin-6 adj2 (inhibit$ or blocker?)).tw. 2. anti-interleukin-6 agent$.tw. 3. interleukin 6 inhibit$ therapy.tw. 4. (tocilizumab or siltuximab or Sarilumab).tw **5. 1 or 2 or 3 or 4** 6. hypertension/ 7. hypertens$.tw. 8. (blood adj pressure).tw. **9. 6 or 7 or 8** 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. Randomized.ab. 13. Placebo.tw. 14. Drug therapy.tw. 15. Randomly.ab. 16. Trial.ab. **17. 10 or 11 or 12 or 13 or 14 or 15or 16** 18. animals/ not (humans/ and animals/) **19. 17 not 18** **20. 5 and 9** 21. **19 and 20**	1. interleukin 6 near/2 (inhibit* or blockade*).ti,ab.kw 2. (anti-interleukin-6 agent*):ti,ab,kw 3. (interleukin 6 inhibitor therapy):ti,ab,w 4. (tocilizumab OR siltuximab OR Sarilumab):ti,ab,kw **5. #1 OR #2 OR #3 OR #4** 6. Hypertension.mp. 7. Hypertens$.tw. 8. (blood adj pressure).tw. **9. #6 OR #7 OR #8** 10. **#5 AND #9**	1. (interleukin-6 adj2 (inhibit$ or blocker?)).tw. 2. anti-interleukin-6 agent$.tw. 3. interleukin 6 inhibit$ therapy.tw. 4. (tocilizumab or siltuximab or Sarilumab).tw **5. 1 or 2 or 3 or 4** 6. hypertension/ 7. hypertens$.tw. 8. (blood adj pressure).tw. **9. 6 or 7 or 8** 10. randomized controlled trial/ 11. Crossover procedure/ 12. Double-blind procedure/ 13. (randomi$ or randomly).tw. 14. (crossover$ or cross-over$).tw. 15. Placebo$.tw. 16. (doubl$ adj blind$).tw. 17. Assign$.ab. 18. Allocat$.ab. 19. Trial.ti. **20. 10 or 11 or 12 or 13 or 14 or 15or 16 or 17 or 18 or 19** 21. (animal$ not (human$ and animal$)).tw. **22. 20 not 21** **23. 5 and 9** 24. **22 and 23**
Methotrexate		
MEDLINE OVID	**Cohrane**	**EMBASE (OVID)**
#1 exp Methotrexate/ #2 amet?opterine.tw. #3 **1 OR 2** #4 hypertension/	#1 methotrexate OR methotrex* OR amethopterin OR methotrexate hydrate OR dicesium salt methotrexate OR	#1 exp Methotrexate/ #2 amet?opterine.tw. #3 **1 OR 2** #4 hypertension/

#5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial.pt. #9 controlled clinical trial.pt. #10 Randomized.ab. #11 Placebo.tw. #12 Drug therapy.tw. #13 Randomly.ab. #14 Trial.ab. #15 **8 or 9 or 10 or 11 or 12 or 13 or 14** #16 animals/ not (humans/ and animals/) #17 **15 not 16** #18 **3 and 7** #19 **17 and 18**	mexate OR sodium salt methotrexate OR disodium salt methotrexate OR MTX OR amethopter* OR mexat* #2 Hypertension.mp. #3 Hypertens$.tw. #4 (blood adj pressure).tw. #5 **#2 OR #3 OR #4** #6 **#1 and #5**	#5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial/ #9 Crossover procedure/ #10 Double-blind procedure/ #11 (randomi$ or randomly).tw. #12 (crossover$ or cross-over$).tw. #13 Placebo$.tw. #14(doubl$ adj blind$).tw. #15 Assign$.ab. #16 Allocat$.ab. #17 Trial.ti. #18 **8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17** #19 (animal$ not (human$ and animal$)).tw. #20 **18 not 19** #21 **3 and 7** #22 **20 and 21**
Interleukin 17 (Anti-IL-17)		
MEDLINE OVID	**Cohrane**	**EMBASE (OVID)**
#1 (interleukin-17 adj2 (Inhibit$ or blockade?)).tw. #2 (Secukinumab OR ixekizumab OR brodalumab).tw. #3 **1 OR 2** #4 hypertension/ #5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial.pt. #9 controlled clinical trial.pt. #10 Randomized.ab. #11 Placebo.tw. #12 Drug therapy.tw. #13 Randomly.ab. #14 Trial.ab. #15 **8 or 9 or 10 or 11 or 12 or 13 or 14** #16 animals/ not (humans/ and animals/) #17 **15 not 16** #18 **3 and 7**	#1 MeSH descriptor: [Interleukin- 17] explode all trees #2 (Secukinumab OR ixekizumab OR brodalumab):TI,AB,KW #3 **#1 OR #2** #4 Hypertension.mp. #5 Hypertens$.tw. #6 (blood adj pressure).tw. #7 **#4 OR #5 OR #6** #8 **#3 AND #7**	#1 (interleukin-17 adj2 (Inhibit$ or blockade?)).tw. #2 (Secukinumab OR ixekizumab OR brodalumab).tw. #3 **1 OR 2** #4 hypertension/ #5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial/ #9 Crossover procedure/ #10 Double-blind procedure/ #11(randomi$ or randomly).tw. #12 (crossover$ or cross-over$).tw. #13 Placebo$.tw. #14 (doubl$ adj blind$).tw. #15 Assign$.ab. #16 Allocat$.ab. #17 Trial.ti. #18 **8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17**

#19 **17 and 18**		#19 (animal$ not (human$ and animal$)).tw. #20 **18 not 19** #21 **3 and 7** #22 **20 and 21**
Anti-IL-1B		
MEDLINE (OVID)	**Cohrane**	**EMBASE (OVID)**
#1 (Interleukin-1beta adj2 (inhibit$ or blocker?)).tw. #2 (Canakinumab or Anakinra).tw. #3 **1 OR 2** #4 hypertension/ #5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial.pt. #9 controlled clinical trial.pt. #10 Randomized.ab. #11 Placebo.tw. #12 Drug therapy.tw. #13 Randomly.ab. #14 Trial.ab. #15 **8 or 9 or 10 or 11 or 12 or 13 or 14** #16 animals/ not (humans/ and animals/) #17 **15 not 16** #18 **3 and 7** #19 **17 and 18**	#1 MeSH descriptor: [Interleukin- 1beta] explode all trees #2 (Canakinumab Or Anakinra):ti,ab,kw #3 **#1 OR #2** #4 Hypertension.mp. #5 Hypertens$.tw. #6 (blood adj pressure).tw. #7 **#4 OR #5 OR #6** #8 **#3 and #7**	#1(Interleukin-1beta adj2 (inhibit$ or blocker?)).tw. #2(Canakinumab or Anakinra).tw. #3 **1 OR 2** #4 hypertension/ #5 hypertens$.tw. #6 (blood adj pressure).tw. #7 **4 or 5 or 6** #8 randomized controlled trial/ #9 Crossover procedure/ #10 Double-blind procedure/ #11 (randomi$ or randomly).tw. #12(crossover$ or cross-over$).tw. #13 Placebo$.tw. #14 (doubl$ adj blind$).tw. #15 Assign$.ab. #16 Allocat$.ab. #17 Trial.ti. #18 **8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17** #19 (animal$ not (human$ and animal$)).tw. #20 **18 not 19** #21 **3 and 7** #22 **20 and 21**
colchicine		
MEDLINE OVID	**Cohrane**	**EMBASE (OVID)**
1. Gout suppressents/or gout 2. colchicine.tw. **3. 1 or 2** 4. hypertension/	1. MeSH descriptor: [Colchicine] explode all trees 2. Hypertension.mp. 3. Hypertens$.tw. 4. (blood adj pressure).tw.	1. Gout suppressents/or gout 2. colchicine.tw. **3. 1 or 2** 4. hypertension/

5. hypertens$.tw. 6. (blood adj pressure).tw. 7. **4 or 5 or 6** 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. Randomized.ab. 11. Placebo.tw. 12. Drug therapy.tw. 13. Randomly.ab. 14. Trial.ab. **15. 8 or 9 or 10 or 11 or 12 or 13 or 14** 16. animals/ not (humans/ and animals/) **17. 15 not 16** **18. 3 and 7** **19. 17 and 18**	**5. #2 OR #3 OR #4** **6. #1 AND #5**	5. hypertens$.tw. 6. (blood adj pressure).tw. 7. **4 or 5 or 6** 8. randomized controlled trial/ 9. Crossover procedure/ 10. Double-blind procedure/ 11. (randomi$ or randomly).tw. 12. (crossover$ or cross-over$).tw. 13. Placebo$.tw. 14. (doubl$ adj blind$).tw. 15. Assign$.ab. 16. Allocat$.ab. 17. Trial.ti. 18. **8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17** 19. (animal$ not (human$ and animal$)).tw. **20. 18 not 19** **21. 3 and 7** **22. 20 and 21**

Appendix B: Characteristics of the included studies

(Caporali et al., 2004)
Design: Randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 21 months
Participants: 72 **Clinical setting:** patients with polymyalgia rheumatica **Mean baseline BP:** Not reported **Age range:** 50-85 **Hypertensive patients (%):** Not reported **Baseline co-morbidities (%):** Not reported
Intervention: Two groups **Co-intervention:** All participants were advised to take calcium and vitamin D supplements.
Adverse effect : Hypertension
Funding Source: The study was funded by the IRCCS Policlinico San Matteo Hospital,
(Van der Veen et al., 1996)
Design: Randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 1 year
Participants: 40 **Clinical setting:** polymyalgia rheumatica and giant cell arteritis **Mean baseline BP: Not reported** **Age range:** 53-84 **Hypertensive patients (%):Not reported** **Baseline co-morbidities (%):Not reported**
Intervention: Two group **Co-intervention:** All patients took prednisone (20 mg/day).
Adverse effect : Hypertension
Funding Source: The study was supported by 'Het Nationaal Reumafonds," The Netherlands.
(Jover et al., 2001)
Design: Randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 24 months
Participants: 42 **Clinical setting:** Giant-Cell Arteritis **Mean baseline BP:** Not reported **Mean range:** 78 **Hypertensive patients (%):** 40.47% **Baseline co-morbidities (%):** DM=125, CVD=4.76
Intervention: Two groups **Co-intervention:** All patients received calcium, 1000 mg/d, and vitamin D3, 600 IU/d.
Adverse effect : Hypertenstion
Funding Source: Fuding by Fondo de Investigacio´n Sanitaria, Spanish Ministry of Health.
(Solomon et al., 2020)
Design: Randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 23 months
Participants: 4786 **Clinical setting:** rheumatoid arthritis. **Mean baseline BP:** Not reported

Median age : 65.0 yeras **Hypertensive patients (%):** 3.76 % **Baseline co-morbidities (%):** Hyperlipidaemia=3.57, DM=2.80%
Intervention: Two group **Co-intervention:** Statin , Aspirin ,Insulin
Adverse effect : Hypertension
Funding Source: supported by the National Institutes of Health
(Strand et al., 1999)
Design: Randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 12 months
Participants: 480 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP:** Not Reported **Mean age :** 54 yeras **Hypertensive patients (%):** Not reported **Baseline co-morbidities (%):** Not reported
Intervention: Three groups **Co-intervention:** NSAIDs, Steroids
Adverse effect : Hypertension
Funding Source: Funded by Hoechst Marion Roussel (HMR)
(Jones et al., 2010)
Design: Randomized, double-blind. **Mean duration of follow-up: 24 WEEKS**
Participants: 673 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 51.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: DMARDs,Anti-TNF blockers**
Adverse effect : Hypertension
Funding Source: funded by F. Hoffmann-La Roche Ltd.
(Bijlsma et al., 2016)
Design: Randomized, double-blind. **Mean duration of follow-up: 2 years**
Participants: 211 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 55 year** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertenstion
Funding Source: funded by Roche Nederland .
(Irle et al., 1985)
Design: Randomized **Mean duration of follow-up: 4 months**
Participants: 56 **Clinical setting: Marrow transplantation** **Mean baseline BP: Not reported** **Age range: 30-47**

Hypertensive patients (%): Not reported **Baseline co-morbidities (%): Not reported**
Intervention: two groups **Co-intervention: Not reported**
Adverse effect : Hypertenstion
Funding Source: funded by National institute of allergy and infections disease.
(De Groot et al., 2005)
Design: Randomized **Mean duration of follow-up: 18 months**
Participants: 100 **Clinical setting: Vasculitis** **Mean baseline BP:Not reported** **Age range: 18-72** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%):Wegener's granulomatosis**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertenstion
Funding Source: Funded by the European union
(Toulmonde et al., 2019)
Design: Randomized, Open lable. **Median duration of follow-up: 23.4 months**
Participants: 72 **Clinical setting: desmoid tumor** **Mean baseline BP: Not reported** **Median age : 42** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): 15.27 % Gardners Syndrome**
Intervention: Two Group **Co-intervention: COX2 Inhibitor,Chemotherapy,Hormonal therapy.**
Adverse effect : Hypertension
Funding Source: funded by GlaxoSmithKline and Novartis
(Drosos et al., 1998)
Design: A prospective randomized **duration of follow-up: 24 months**
Participants: 103 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 51.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: University of Ioaunina medical school
(Keystone et al., 2011)
Design: Randomized, double-blind. **duration of follow-up: 12 weeks**
Participants: 201 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Age range: 34-75** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joint count**

(Edwards et al., 2004)
Design: Randomized, double-blind. **duration of follow-up: 48 weeks**
Participants: 80 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 54** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joints**
Intervention: Two groups **Co-intervention: Anti-rheumatic drugs**
Adverse effect : Hypertension
Funding Source: Funded by Roche
Intervention: Four groups **Co-intervention: COX-2 Inhibitors, Glucocorticoids**
Adverse effect : Hypertension
Funding Source: Funded by Chelsea Therapeutics International Ltd

(Emery et al., 2000)
Design: Randomized, double-blind. **duration of follow-up: 1 year**
Participants: 612 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 58.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: NSAIDs. DMARD treatment**
Adverse effect : Hypertension
Funding Source: British society for rheumatology
(Ferraccioli et al., 2002)
Design: Randomized, Open label. **Duration of follow-up: 36 months**
Participants: 126 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 59** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: three groups **Co-intervention: Prednisone, Antimalarials**
Adverse effect : Hypertension
Funding Source: Funded by University of Udine
(Ishaq et al., 2011)
Design: Randomized, double-blind. **Duration of follow-up: 1 year**
Participants: 240 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported**

Mean age : 58.3 **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two group **Co-intervention: NSAID,Steriod**
Adverse effect : Hypertension
Funding Source: Not reported

(Barker et al., 2011)
Design: Randomized, Open label. **Mean duration of follow-up: 6 months**
Participants: 868 **Clinical setting: plaque psoriasis** **Mean baseline BP: Not reported** **Age range: 18-78** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Schering-Plough Research Institute.
(Su et al., 2009)
Design: Randomized, Single-Blind **Mean duration of follow-up: 1 year**
Participants: 17 **Clinical setting: Systemic Sclerosis** **Mean baseline BP: 123/69 mmHg** **Mean age : 52.8** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by the Oxnard Foundation.
(Keystone, 2005)
Design: Randomized, double-blind. **Mean duration of follow-up: 6 months**
Participants: 80 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 54** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Not reported
(Le Loet et al., 2008)
Design: Randomized, Open label **Mean duration of follow-up: 9 months**
Participants: 1186 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported**

Age range: 20-86 **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Anti-Rheumatic drugs**
Adverse effect : Hypertension
Funding Source: Funded by Amgen Inc.,

(Marchesoni et al., 2002)
Design: Randomized **Mean duration of follow-up: 24 months**
Participants: 49 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 49.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Corticosteroids**
Adverse effect : Hypertension
Funding Source: Not reorted
(Metzler et al., 2007)
Design: Randomized, Open label **Duration of follow-up: 24 months**
Participants: 54 **Clinical setting: Wegener's granulomatosis** **Mean baseline BP: Not reported** **Age range: 27-76** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Prednisolone**
Adverse effect : Hypertension
Funding Source: Sanofi Aventis and Wyeth companies
(Naeini et al., 2020)
Design: Randomized **Duration of follow-up: 6 months**
Participants: 33 **Clinical setting: lichen planopilaris** **Mean baseline BP: Not reported** **Mean age : 46.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%):Telangiectasia**
Intervention: Two groups **Co-intervention: Mycophenolate mofetil, Hydroxychloroquine**

Adverse effect : Hypertension
Funding Source: NOt received any funding.
(Strand et al., 1999)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 482 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 54** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Hoechst marion roussel

(Takeuchi et al., 2021)
Design: Randomized **Mean duration of follow-up: 1 year**
Participants: 550 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 50** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Pfizer
(van der Heijde et al., 2006)
Design: Randomized, double-blind **Duration of follow-up: Two years**
Participants: 451 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Meange : 52.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Wyeth Research
(Sieper et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: Three months**
Participants: 192 **Clinical setting: Axial Spondyloarthritis** **Mean baseline BP: Not reported** **Mean age : 38**

Hypertensive patients (%): Not reported **Baseline co-morbidities : Inflammatory bowel disease**
Intervention: TWO groups **Co-intervention: DMARD, NSAID**
Adverse effect : Hypertension
Funding Source: Funded by Abbott Laboratories
(Anthony A. Amato and Richard Barohn, 2011)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 16 **Clinical setting:** Dermatomyositis **Mean baseline BP: Not reported** **Meana age : 44.2** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: NIH National Institute of Neurological Disorders and Stroke

(Smolen et al., 2009a)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 619 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 52.2** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Tuberculosis**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(Butchart et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 41 **Clinical setting: Alzheimer disease** **Mean baseline BP: Not reported** **Mean age : 72.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Pfizer Pharmaceuticals
(Smolen et al., 2015)

Design: Randomized, double-blind **Duration of follow-up: Two years**
Participants: 451 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Meange : 52.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Wyeth Research
(Deodhar et al., 2019)
Design: Randomized, double-blind **Duration of follow-up: 52 weeks**
Participants: 317 **Clinical setting:** Spondyloarthritis **Mean baseline BP: Not reported** **Mean age : 37.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: NSAIDs,Dmards.**
Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(Emery et al., 2009)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 478 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Meange : 52.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Hydroxychloroquine,Sulfasalazine,Leflunomide**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development, Inc.
(Smolen et al., 2009b)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 461 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 55** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Hydroxychloroquine**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development and Schering-Plough Research Institute..
(Weinblatt et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: 3 months**

Participants: 592 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 51.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Anti-Inflammatory**
Adverse effect : Hypertension
Funding Source: Funded by Janssen Research & Development LLC, and Merck
(Gottlieb et al., 2003)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 112 **Clinical setting: Psoriasis** **Mean baseline BP: Not reported** **Mean age : 48.2** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX,Corticosteroids**
Adverse effect : Hypertension
Funding Source: Funded by Immunex Corp,A Subsidiary of Amgen Inc.

(Grant et al., 2010)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 33 **Clinical setting:** hidradenitis suppurativa **Mean baseline BP: Not reported** **Mean age : 34** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Not reported
(Yamamoto et al., 2014a)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 230 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 56** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**

Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(Holgate et al., 2011)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 131 **Clinical setting: Asthma** **Mean baseline BP: Not reported** **Mean age : 48.67** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Allergy**
Intervention: Two groups **Co-intervention: Corticosteroids**
Adverse effect : Hypertension
Funding Source: Funded by Wyeth
(Aitken et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 84 **Clinical setting:** erosive hand OsteoaRthritis **Mean baseline BP: Not reported** **Mean age : 63.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: COX-2inhibitors**
Adverse effect : Hypertension
Funding Source: Funded by AbbVie Pty Ltd.

(Yamamoto et al., 2014b)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 316 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 66** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Four groups **Co-intervention: Corticosteroid**
Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(Judson et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 11 months**
Participants: 173 **Clinical setting: Sarcoidosis** **Mean baseline BP: Not reported** **Mean age : 50** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**

Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by the National Institutes of Health
(Kavanaugh et al., 2009)
Design: Randomized **Duration of follow-up: 6 months**
Participants: 405 **Clinical setting: Psoriatic** Arthritis **Mean baseline BP: Not reported** **Mean age : 48.2** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Corticosteroids**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development,Inc.
(Van de Kerkhof et al., 2008)
Design: Randomized, Open label **Duration of follow-up: 3 months**
Participants: 142 **Clinical setting: Plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 45.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Wyeth Pharmaceuticals

(Keystone et al., 2008)
Design: Randomized, double-blind **Duration of follow-up: 1 years**
Participants: 982 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 52.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Wyeth
(Landewé et al., 2014)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 325 **Clinical setting: ankylosing spondylitis** **Mean baseline BP: Not reported** **Mean age : 63.6**

Hypertensive patients (%): Not reported **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: NSAIDs,DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(Cai et al., 2017)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 425 **Clinical setting: Plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 43.2** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention:** Acitretin, MTX
Adverse effect : Hypertension
Funding Source: Funded by AbbVie Inc.
(Maini et al., 1999)
Design: Randomized, double-blind **Duration of follow-up: 7 months**
Participants: 428 **Clinical setting:** Rheumatoid Arthritis **Mean baseline BP: Not reported** **Mean age : 51** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: NSAIDs,Corticoseroids**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Inc.

(Mease et al., 2005)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 313 **Clinical setting: Psoriatic Arthritis** **Mean baseline BP: Not reported** **Mean age : 56.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Spondylitis, Arthritis mutilans**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Abbott Laboratories.
(Menter et al., 2007)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 834

Clinical setting: Plaque psoriasis **Mean baseline BP: Not reported** **Mean age : 45.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Biologic agents,MTX,Acitretin,Cyclosporin**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Inc.
(Regueiro et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 19 months**
Participants: 301 **Clinical setting: Crohn's Disease** **Mean baseline BP: Not reported** **Mean age : 69** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Abscess,Internal fistula**
Intervention: Two groups **Co-intervention: Anti-Tumor necrosis factor**
Adverse effect : Hypertension
Funding Source: Funded by Janssen Research & Development, LLC.
(Hall III et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 20 **Clinical setting: pemphigus vulgaris** **Mean baseline BP: Not reported** **Mean age : 54.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%):**
Intervention: Two groups **Co-intervention: Prednisone**
Adverse effect : Hypertension
Funding Source: Funded by Autoimmunity Centers of Excellence

(Salvarani et al., 2007)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 51 **Clinical setting: Polymyalgia Rheumatica** **Mean baseline BP: Not reported** **Mean age : 47.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development, Inc..
(Schiff et al., 2014)
Design: Randomized, double-blind **Duration of follow-up: 3 months**

Participants: 37 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 59** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: MTX**
Adverse effect : Hypertension
Funding Source: Funded by biopharmaceutical company (UCB)
(van Vollenhoven et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 73 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 56.7** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX,DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Pfizer
(Westhovens et al., 2006)
Design: Randomized. **Duration of follow-up: 6 months**
Participants: 751 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 53** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs,Corticoteroids**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development, Inc

(Gabay et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 324 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 54.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension

Funding Source: Not reported
(Combe et al., 2006)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 153 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 53.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Wyeth
(Giles et al., 2020)
Design: Randomized, open-label **Duration of follow-up: 4.5 years**
Participants: 3080 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 61** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): CVD**
Intervention: Two groups **Co-intervention: Anti-malarials,MTX,Sulfasazine,NSAIDs,Glucocorticoids**
Adverse effect : Hypertension
Funding Source: Funded by F. Hoffmann-La Roche Ltd.
(Barker et al., 2011)
Design: Randomized, open-label **Duration of follow-up: 6 months**
Participants: 868 **Clinical setting: plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 41.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities :lymphoproliferative disease**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Schering-Plough Research Institute.

(McInnes et al., 2020)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 853 **Clinical setting: psoriatic arthritis** **Mean baseline BP: Not reported** **Mean age : 49.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**

Adverse effect : Hypertension
Funding Source: funded by Novartis Pharma
(Burmester et al., 2017a)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 369 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 53.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Sanofi Genzyme and Regeneron Pharmaceuticals.
(Taylor et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 559 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 52.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Janssen Global Services and GlaxoSmithKline.
(Takeuchi et al., 2021)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 540 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 59** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Pfizer

(van der Heijde et al., 2006)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 451 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 59** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**

Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Wyeth Research,
(Kremer et al., 2004)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 263 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Age average : 18-75** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Aventis Pharmaceuticals.
(Beissert et al., 2010)
Design: Randomized, double-blind **Duration of follow-up: 13 months**
Participants: 94 **Clinical setting: Pemphigus Vulgaris** **Mean baseline BP: Not reported** **Median age : 46** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Vifor
(Schiff et al., 2010)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 1282 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 56.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by by Roche Products Ltd.

(Smolen, 1999)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 37 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported**

Mean age : 58.9 **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: DMARDs,Corticosteroids,NSAIDs**
Adverse effect : Hypertension
Funding Source: Not reported
(Strand et al., 1999)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 482 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 54.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Hoechst Marion Roussel (HMR)
(Becker et al., 2008)
Design: Randomized, open-label **Duration of follow-up: 3 months**
Participants: 602 **Clinical setting: Liver transplantation** **Mean baseline BP: Not reported** **Mean age : 53.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Steroids**
Adverse effect : Hypertension
Funding Source: Funded by Astellas Pharma
(Beissert et al., 2009)
Design: Randomized, open-label **Duration of follow-up: 3 months**
Participants: 53 **Clinical setting: Plaque Psoriasis** **Mean baseline BP: (129-81)(130-82)** **Mean age : 42.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Roche

(Boudjema et al., 2011)
Design: Randomized. **Duration of follow-up: 12 months**

Participants: 195 **Clinical setting: Liver transplantation** **Median baseline BP: 120-70** **Median age : 52** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by French Ministry of Health
(Emery et al., 2009)
Design: Randomized, double-blind **Duration of follow-up: 13 months**
Participants: 612 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 50.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Centocor Research and Development, Inc
(Gheith et al., 2007)
Design: Randomized. **Duration of follow-up: 3 months**
Participants: 475 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 34.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Nephrosclerosis**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Not reported
(Ioannides et al., 2012)
Design: Randomized. **Duration of follow-up: 6 months**
Participants: 47 **Clinical setting: pemphigus** **Mean baseline BP: Not reported** **Mean age : 53.7** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: None
(Ishaq et al., 2011)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 180

Clinical setting: Rheumatoid arthritis **Mean baseline BP: Not reported** **Mean age : 58.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Not reported
(Kahaly et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 9 months**
Participants: 164 **Clinical setting: Graves' orbitopathy** **Mean baseline BP: Not reported** **Mean age : 52.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Graves disease**
Intervention: Two groups **Co-intervention: Antithyroid**
Adverse effect : Hypertension
Funding Source: Funded by Novartis
(Kahan, 2000)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 709 **Clinical setting: Renel allograft rejection** **Mean baseline BP: Not reported** **Mean age : 46.8** **Hypertensive patients (%): 29%** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not repeated**
Adverse effect : Hypertension
Funding Source: Funded by National Institute of Diabetes and Digestive and Kidney Diseases.
(Karanikolas et al., 2006)
Design: Randomized, open label **Duration of follow-up: 1 year**
Participants: 71 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 49** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not repprted**
Adverse effect : Hypertension
Funding Source: Not reported

(Metzler et al., 2007)
Design: Randomized. **Duration of follow-up: 3 months**

Participants: 54 **Clinical setting: Wegener's granulomatosis** **Mean baseline BP: Not reported** **Mean age : 55** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Bundesministerium fu¨ r Bildung und Forschung
(Najarian et al., 1985)
Design: Randomized. **Duration of follow-up: 3 months**
Participants: 230 **Clinical setting: Renal Allograft** **Mean baseline BP: Not reported** **Mean age : 35** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Diabetic 21%**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Not reported
(Tedesco-Silva et al., 2007)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 271 **Clinical setting: Renal transplantation** **Mean baseline BP: Not reported** **Mean age : 44.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharmaceuticals Corporation.
(De Simone et al., 2009)
Design: Randomized, open label **Duration of follow-up: 6 months**
Participants: 145 **Clinical setting: Liver transplantation** **Mean baseline BP: Not reported** **Mean age : 57.8** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharma.

(Sticherling et al., 2017)
Design: Randomized. **Duration of follow-up: 12 months**
Participants: 54 **Clinical setting: bullous pemphigoid** **Mean baseline BP: Not reported** **Mean age : 79** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Riemser Inc.
(Sundel et al., 2012)
Design: Randomized. **Duration of follow-up: 6 months**
Participants: 364 **Clinical setting: lupus nephritis** **Mean baseline BP: Not reported** **Mean age : 33** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Diabetic 21%**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Aspreva Pharmaceuticals Corporation
(Takahashi et al., 2013)
Design: Randomized,open label **Duration of follow-up: 12 months**
Participants: 122 **Clinical setting: Renal transplantation** **Mean baseline BP: Not reported** **Mean age : 42.5** **Hypertensive patients (%): 3.3%** **Baseline co-morbidities (%): Diabetic 8.2%**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis
(Vitko et al., 2006)
Design: Randomized,open label **Duration of follow-up: 6 months**
Participants: 977 **Clinical setting: Kidney transplantation** **Mean baseline BP: Not reported** **Mean age : 47.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Diabetic 21%**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Fujisawa GmbH

(Yunyun et al., 2019)
Design: Randomized,open label **Duration of follow-up: 12 months**
Participants: 59 **Clinical setting: immunoglobulin G4-related disease** **Mean baseline BP: Not reported** **Mean age : 56.76** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Diabetic 21%**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by National Natural Science Foundation of China
(Poiley et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 83 **Clinical setting: Gout** **Mean baseline BP: Not reported** **Mean age : 53.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Three groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by CymaBay Therapeutics
(Terkeltaub et al., 2010)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 185 **Clinical setting: Gout flare** **Mean baseline BP: Not reported** **Mean age : 51.9** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by URL Pharma
(Pakfetrat et al., 2010)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 34 **Clinical setting: Aphthous stomatitis** **Mean baseline BP: Not reported** **Mean age : 33.11** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**

Adverse effect : Hypertension
Funding Source: Not reported

(Schlesinger et al., 2011)
Design: Randomized, double-blind **Duration of follow-up: 4 months**
Participants: 432 **Clinical setting: Gout** **Mean baseline BP: Not reported** **Mean age : 54.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharma
(Alten et al., 2011)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 274 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 61.02** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Swollen joints**
Intervention: Two groups **Co-intervention: DMARDs,MTX**
Adverse effect : Hypertension
Funding Source: Funded by BioMed Central Ltd.
(Choudhury et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 189 **Clinical setting: Atherosclerosis and Type 2 Diabetes or Glucose Intolerance** **Mean baseline BP: (128.7-76.6)(128.4-76.9)** **Mean age : 61.9** **Hypertensive patients (%): 82%** **Baseline co-morbidities (%): Diabetes,Cholesterol**
Intervention: Two groups **Co-intervention: ACE inhibitor,Beta-blocker,Statin,Insulin and Antiplatelet agent.**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.
(Ridker et al., 2012)
Design: Randomized, double-blind **Duration of follow-up: 4 months**
Participants: 551 **Clinical setting: atherothrombosis** **Mean baseline BP: (128-78)** **Mean age : 55.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**

Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharma

(Russell et al., 2019)
Design: Randomized, double-blind **Duration of follow-up: 12 months**
Participants: 38 **Clinical setting: peripheral artery disease** **Mean baseline BP: (129.7-74.2)(141.6-76.2)** **Mean age : 66** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharma
(Schiff et al., 2004)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 1399 **Clinical setting: Rheumatoid Arthritis** **Mean baseline BP: Not reported** **Mean age : 57.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Amgen, Inc
(Sheng et al., 2020)
Design: Randomized, double-blind **Duration of follow-up: 5 months**
Participants: 45 **Clinical setting: deterioration of cardiac and respiratory function in SARS-CoV-2** **Mean baseline BP: Not reported** **Mean age : 54.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Stroke,Coronary Artery disease, Atrial fibrillation.**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis Pharma
(Burmester et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 1162 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 51.2** **Hypertensive patients (%): Not reported**

Baseline co-morbidities : Swollen joint pain
Intervention: Two groups **Co-intervention: DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Roche

(Khanna et al., 2016)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 87 **Clinical setting: systemic sclerosis** **Mean baseline BP: Not reported** **Mean age : 51** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Immunosuppressive drugs**
Adverse effect : Hypertension
Funding Source: Funded by F Hoffmann-La Roche, Genentech.
(Tanaka et al., 2019)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 243 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 56.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Sanofi and Regeneron Pharmaceuticals, Inc.
(Fleischmann et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: 2 year**
Participants: 1195 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 52** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Abbott, BMS, Genentech, Janssen, Pfizer, and UCB
(Nasonov et al., 2020)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 428 **Clinical setting: Rheumatoid arthritis**

Mean baseline BP: Not reported **Mean age : 51.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by R-Pharm

(Van Rhee et al., 2014)
Design: Randomized, double-blind **Duration of follow-up: 5 months**
Participants: 79 **Clinical setting: Castleman's disease** **Mean baseline BP: Not reported** **Mean age : 56.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Corticosteriods,Chemotherapy,Interferon**
Adverse effect : Hypertension
Funding Source: Funded by Janssen Research & Development.
(Yazici et al., 2012)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 619 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 55.8** **Hypertensive patients (%): 38.2** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: DMARDs,Anti-TNF**
Adverse effect : Hypertension
Funding Source: Funded by Roche
(Aletaha et al., 2017)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 878 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 55.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, DMARDs**
Adverse effect : Hypertension
Funding Source: Funded by Janssen Research & Development, LLC, and GlaxoSmithKline.
(Smolen et al., 2008)
Design: Randomized, double-blind **Duration of follow-up: 6 months**

Participants: 622 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 51.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joint**
Intervention: Two groups **Co-intervention: MTX, DMARDs,Steroids,NSAIDs,Anti-TNF**
Adverse effect : Hypertension
Funding Source: Funded by Roche.

(Genovese et al., 2008)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 1216 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 54** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, Hydroxychloroquine,Sulfasalazine,Leflunomide,Azathioprine,NSAIDs**
Adverse effect : Hypertension
Funding Source: Funded by Roche
(Bingham et al., 2015)
Design: Randomized. **Duration of follow-up: 3 months**
Participants: 91 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **age average : 18-64** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Roche.
(Papp et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: 9 months**
Participants: 125 **Clinical setting: plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 46.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: UV therapy, Biologic therapy**
Adverse effect : Hypertension
Funding Source: Funded by Novartis and other pharmaceutical companies
(Braun et al., 2017)

Design: Randomized. **Duration of follow-up: 2 years**
Participants: 371 **Clinical setting: Ankylosing spondylitis** **Mean baseline BP: Not reported** **Mean age : 42.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, Sulfasalazine,Glucocorticoids**
Adverse effect : Hypertension
Funding Source: Funded by Novartis

(Deodhar et al., 2021)
Design: Randomized, double-blind **Duration of follow-up: 13 months**
Participants: 555 **Clinical setting: Nonradiographic Axial Spondyloarthritis** **Mean baseline BP: Not reported** **Mean age : 39.80** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis
(Dokoupilová et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 240 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 55.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, DMARDs,Leflunomide**
Adverse effect : Hypertension
Funding Source: Funded by Novartis
(Huang et al., 2020)
Design: Randomized, double-blind **Duration of follow-up: 4 months**
Participants: 606 **Clinical setting: Ankylosing spondylitis** **Mean baseline BP: Not reported** **Mean age : 35.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities (%): Not reported**
Intervention: Two groups **Co-intervention: MTX, Sulfasalazine,Corticosteroid**
Adverse effect : Hypertension

Funding Source: Funded by Novartis
(Mease et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 606 **Clinical setting: Psortiatic arthritis** **Mean baseline BP: Not reported** **Mean age : 49.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities :Dactylitis ,Enthesitis**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.

(Paul et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 182 **Clinical setting: Psoriasis** **Mean baseline BP: Not reported** **Mean age : 46.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: Biologic agent,Conventional agent**
Adverse effect : Hypertension
Funding Source: Funded by Novartis
(Kivitz et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 4 months**
Participants: 350 **Clinical setting: Ankylosing spondylitis** **Mean baseline BP: Not reported** **Mean age : 56.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Back pain**
Intervention: Two groups **Co-intervention: MTX, Sulfasalazine,Corticosteroid,NSAID**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.
(Langley et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 142 **Clinical setting: plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 46.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Back pain**
Intervention: Two groups **Co-intervention: Not reported**

Adverse effect : Hypertension
Funding Source: Funded by Eli Lilly
(Mease et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 996 **Clinical setting: psoriatic arthritis** **Mean baseline BP: Not reported** **Mean age : 49** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joint**
Intervention: Two groups **Co-intervention: MTX,Corticosteroid,**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.

(Nash et al., 2017)
Design: Randomized, double-blind **Duration of follow-up: 6 months**
Participants: 363 **Clinical setting: psoriatic arthritis** **Mean baseline BP: Not reported** **Mean age : 52.6** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joint**
Intervention: Two groups **Co-intervention: DMARDs,MTX**
Adverse effect : Hypertension
Funding Source: Funded by Eli Lilly.
(Papp et al., 2014a)
Design: Randomized, open-label **Duration of follow-up: 2.5 years**
Participants: 181 **Clinical setting: psoriasis** **Mean baseline BP: Not reported** **Mean age : 43.1** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.
(Pavelka et al., 2015)
Design: Randomized, double-blind **Duration of follow-up: 4 months**
Participants: 252 **Clinical setting: Rheumatoid arthritis** **Mean baseline BP: Not reported** **Mean age : 53** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Swollen joint**

Intervention: Two groups **Co-intervention: MTX,Corticosteroid**
Adverse effect : Hypertension
Funding Source: Funded by Amgen Inc.
(Rich et al., 2013)
Design: Randomized, double-blind **Duration of follow-up: 8 months**
Participants: 404 **Clinical setting: plaque psoriasis** **Mean baseline BP: Not reported** **Mean age : 44.5** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: UV therapy,Biologic therapy**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.

(Ryan et al., 2018)
Design: Randomized, double-blind **Duration of follow-up: 3 months**
Participants: 149 **Clinical setting: genital psoriasis** **Mean baseline BP: Not reported** **Mean age : 44.4** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Psoriasis**
Intervention: Two groups **Co-intervention: Biological therapy**
Adverse effect : Hypertension
Funding Source: Funded by Eli Lilly.
(Tahir et al., 2017)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 637 **Clinical setting: Rheumatoid Arthritis** **Mean baseline BP: Not reported** **Mean age : 53.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: MTX, DMARDs,Leflunomide**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.
(Bagel et al., 2021)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 1102 **Clinical setting: Plaque psoriasis** **Mean baseline BP: Not reported**

Mean age : 49.3 **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: Not reported**
Adverse effect : Hypertension
Funding Source: Funded by Novartis.
(Paul et al., 2019)
Design: Randomized, double-blind **Duration of follow-up: 1 year**
Participants: 301 **Clinical setting: psoriatic plaques** **Mean baseline BP: Not reported** **Mean age : 53.3** **Hypertensive patients (%): Not reported** **Baseline co-morbidities : Not reported**
Intervention: Two groups **Co-intervention: Biologic therapy**
Adverse effect : Hypertension
Funding Source: Funded by Eli Lilly.

(Belani et al., 2022)
Design: Randomized, open-lable **duration of follow-up:** 24 weeks
Participants: 136 **Clinical setting: Rheumatoid Arthritis** **Mean baseline BP:** Not reported **Median age range: 39** **Hypertensive patients (%):** Not reported **Baseline co-morbidities (%):** Not reported
Intervention: Two groups **Co-intervention**: Not reported
Adverse effect : Hypertension
Funding Source: The study was funded by Institute Ethics Committee
(Behrens et al., 2022)
Design: Randomized, double-blind, placebo-controlled trial **duration of follow-up: 24 weeks**
Participants: 204 **Clinical setting:** spondyloarthritis **Mean baseline BP:** Not reported **Mean age range: 47.8** **Hypertensive patients (%):** Not reported **Baseline co-morbidities (%):** Not reported
Intervention: Two groups **Co-intervention**: NSAID,DMARD,Oral corticosteroid
Adverse effect : Hypertension
Funding Source: The study was funded by the Novartis

Appendix C: Methodological quality of included studies:

(Caporali et al., 2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random selection used and all patients assessed for eligibility included in study
Allocation concealment (selection bias)	Low Risk	Block balancing used in allocation. No centre stratification.
Blinding of participants and personnel (performance bias)	Low Risk	Personnel and participants blinded
Blinding of outcome assessment (detection bias)	Low Risk	Study double blinded. Formal blinding assessment not done.
Incomplete outcome data (attrition bias)	Low Risk	Six lost to follow-up and excluded. This represented less than 20 percent of withdrawals.
Selective reporting (reporting bias)	Low Risk	Outcomes listed in methods section were all reported in results.
Other bias	Unclear Risk	High prednisone as a starting dose and a high dose of folic acid could have contributed to the reported observed effects.

(Irle et al., 1985)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of randomization sequence not described in sufficient detail
Allocation concealment (selection bias)	Low risk	Concealment scheme implemented
Blinding of participants and personnel (performance bias)	Low risk	All Participants and personnel blinded apart from protocol registrar
Blinding of outcome assessment (detection bias)	Unclear risk	No blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	No exclusions and data complete for all outcomes and participants
Selective reporting (reporting bias)	Low risk	All outcomes listed in methods section were reported
Other bias	Unclear risk	No stratification on basis of diagnosis providing an incomparable patient population

(Jones et al., 2010)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	Methods used to randomized not described
Allocation concealment (selection bias)	Unclear risk of bias	Concealment scheme not described in 'Methods' section but likely concealment was done
Blinding of participants and personnel (performance bias)	Low risk	Double blind, double dummy study design
Blinding of outcome assessment (detection bias)	Low risk	Double dummy design therefore participants and personnel were blinded sufficiently

Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each of three groups were reported
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other bias detected

(Bijlsma et al., 2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomization sequence generation method was described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods sections were reported
Other bias	Low risk	No other bias detected

(van der Heijde et al., 2006)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence allocation method described in detail.
Allocation concealment (selection bias)	Unclear risk	No sufficient detailing of concealment scheme or stratification.

Blinding of participants and personnel (performance bias)	Low Risk	All patients and investigators blinded to study treatment.
Blinding of outcome assessment (detection bias)	Low risk	All investigators blinded to treatment. No formal blinding assessment.
Incomplete outcome data (attrition bias)	Unclear risk	Uneven numbers of withdrawals. Reasons provided include adverse events, lack of efficacy, protocol violation and patient request or death in course of study. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Inter-reader variability assessed. All outcomes listed in methods reported.
Other bias	Low risk	No other bias detected

(Takeuchi et al., 2021)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocation sequence described without detailing of sequencing method
Allocation concealment (selection bias)	Unclear risk	No details on concealment scheme
Blinding of participants and personnel (performance bias)	Low Risk	Double blinding of personnel and participants conducted
Blinding of outcome assessment (detection bias)	Low Risk	Double blinding of personnel and participants.
Incomplete outcome data (attrition bias)	Low risk	Attritions and exclusions reported and linear inter/extrapolation and last-observation-carried-forward methods used to impute missing data.

Selective reporting (reporting bias)	Low Risk	Outcomes listed in methods section all reported
Other bias	Low risk	No other bias detected

(Strand et al., 1999)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential randomization schedule using block size of 3. Unclear detail on generation of schedule
Allocation concealment (selection bias)	Low risk	Time stratification used.
Blinding of participants and personnel (performance bias)	Low risk	Oral dose of leflunomide and its matching placebo once daily combined with oral dose methotrexate and its placebo once weekly.
Blinding of outcome assessment (detection bias)	Low risk	Blinding maintained to the end of study
Incomplete outcome data (attrition bias)	Low risk	Same reasons for missing data across the three groups; data imputed using last observation carried forward method.
Selective reporting (reporting bias)	Low risk	Study protocol available. All outcomes listed in method reported.
Other bias	Low risk	No other bias detected

(Solomon et al., 2020)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence derived from results of active run-in phase conducted for all participants
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinded. Drug dosing unclear in regards to taste and appearance

Blinding of outcome assessment (detection bias)	Low risk	Central computerized drug-dosing algorithm used
Incomplete outcome data (attrition bias)	Low risk	Pre-specified secondary analyses used for incomplete outcome data
Selective reporting (reporting bias)	Low risk	All outcomes listed within the methods were reported
Other bias	Unclear risk	Occurrence of adverse events was conducted every 4-12 weeks, leaving the likelihood that patients could have experienced these in between the study visits and failed to mention them or exaggerated during the visit.

(Naeini et al., 2020)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	Randomization allocation applied
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Similar reasons for missing outcomes, proportion of missing outcomes when compared to observed adverse events not sufficient to impose a clinically relevant impact
Selective reporting (reporting bias)	Low risk	All outcomes listed within the methods were reported
Other bias	Low risk	No other bias detected

(Metzler et al., 2007)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Sequence generation process using exclusion criteria based on results of a series of tests
Allocation concealment (selection bias)	Low risk	Random assignment to treatments
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding or lack thereof
Blinding of outcome assessment (detection bias)	High risk	No blinding outcome assessment
Incomplete outcome data (attrition bias)	High risk	Imbalance in proportion of missing outcomes for interventions (2 in MTX-limb and 6 in LEF-limb)
Selective reporting (reporting bias)	Low risk	All primary outcomes reported
Other bias	Low risk	No other bias detected

(Marchesoni et al., 2002)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	First phase open and uncontrolled, second phase (primary phase) randomized.
Allocation concealment (selection bias)	Low risk	Randomized allocation to intervention groups
Blinding of participants and personnel (performance bias)	High risk	Single blinding (only assessors were unaware of the therapy)
Blinding of outcome assessment (detection bias)	Low risk	Assessors unaware of therapy and mutually agreed on scores to be used
Incomplete outcome data (attrition bias)	High risk	High withdrawal rate in one intervention (14 out of 22 taking CSA) with proportion of missing outcomes enough to have clinically relevant impact on the

		estimation of the effect of the intervention
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods section were all reported
Other bias	High risk	Baseline imbalance present

(Le Loet et al., 2008)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details
Allocation concealment (selection bias)	Unclear risk	Insufficient details
Blinding of participants and personnel (performance bias)	Low risk	Open label study- no blinding
Blinding of outcome assessment (detection bias)	Low risk	Open label study- no blinding
Incomplete outcome data (attrition bias)	Low risk	Reason for withdrawal reported. Similar proportion of patients reported to have withdrawn from each group.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in methods.
Other bias	Low risk	No other bias detected

(Su et al., 2009)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All eligible patients included
Allocation concealment (selection bias)	Low risk	Randomized allocation using computer-generated randomization schedule

Blinding of participants and personnel (performance bias)	High risk	Single blind design (participants not aware of the treatment protocol)
Blinding of outcome assessment (detection bias)	High risk	No blinding of personnel and assessors involved in study
Incomplete outcome data (attrition bias)	Low risk	Equal proportion of withdrawals for both groups. Completer analysis used to balance outcome data
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods match those in results
Other bias	High risk	No placebo group, making results limited to the study and not replicable to other populations

(Jover et al., 2001)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation based on results of inclusion criteria
Allocation concealment (selection bias)	Low risk	Random assignment in blocks of six
Blinding of participants and personnel (performance bias)	Low risk	Identical active and placebo drugs in regards to their physical characteristics
Blinding of outcome assessment (detection bias)	Low risk	Assessment of outcomes carried out by physician without contact with patients
Incomplete outcome data (attrition bias)	High risk	Unequal withdrawal across groups (3 in control group and 6 in intervention group)
Selective reporting (reporting bias)	Low risk	All outcomes included in methods reported in results
Other bias	Unclear risk	Very small sample size

(Barker et al., 2011)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Randomization through a central call centre
Allocation concealment (selection bias)	Low risk	Randomization through a central call centre for assignment to groups
Blinding of participants and personnel (performance bias)	Low risk	Double blinded
Blinding of outcome assessment (detection bias)	Low risk	Double blinded
Incomplete outcome data (attrition bias)	High risk	Significant differences in proportion of those that completed (83% in infliximab and 59% in MTX group)
Selective reporting (reporting bias)	Low risk	All outcomes in methods included in results
Other bias	High risk	All the authors had financial ties to drug manufacturing companies and firms conducting clinical trials

(Ishaq et al., 2011)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No detailing of the random sequencing used
Allocation concealment (selection bias)	Unclear risk	Random sequencing. No detailing of how the sequence was arrived at.
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinded. No further information provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Double blinded. No further information provided
Incomplete outcome data (attrition bias)	Low risk	Withdrawal numbers accounted for. Proportion of withdrawals in each groups not sufficient to affect the measure of the impact of interventions in both groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes in methods similar to those in results

Other bias	Low risk	No other risks detected

(Ferraccioli et al., 2002)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No sufficient information on randomization sequence
Allocation concealment (selection bias)	Unclear risk	Random allocation. No details on sequence used
Blinding of participants and personnel (performance bias)	High risk	Patients managed in open fashion
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Outcomes included in methods also included in results
Other bias	Low risk	No other detected bias

(Emery et al., 2000)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized. No details of the randomization sequence
Allocation concealment (selection bias)	Unclear risk	Randomized. No details of the randomization sequence
Blinding of participants and personnel (performance bias)	Low risk	Double blinded. Drug dosage provided once daily and once weekly
Blinding of outcome assessment (detection bias)	Low risk	Double blinded study. Radiographs blinded and read separately.

Incomplete outcome data (attrition bias)	Low risk	Numbers of withdrawn participants provided. Proportion of incomplete data in either group not sufficient to affect the measure of the effect of the intervention
Selective reporting (reporting bias)	Low risk	All outcomes included in methods reported in results
Other bias	Low risk	No other bias detected

(Edwards et al., 2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised without further details
Allocation concealment (selection bias)	Unclear risk	Randomized without further details
Blinding of participants and personnel (performance bias)	Low risk	Both patients and investigators blinded to assigned medications
Blinding of outcome assessment (detection bias)	Low risk	All personnel kept blinded even during patient review visits on site
Incomplete outcome data (attrition bias)	Low risk	Adequate withdrawal information provided. Data imputed for all patients that withdrew from study using a last observation carried forward method.
Selective reporting (reporting bias)	Low risk	Study protocol included. Outcomes included in methods also reported in results.
Other bias	Low risk	No other biases detected

(Keystone et al., 2011)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Randomized without further details
Allocation concealment (selection bias)	Low risk	Random assignment to one of four groups.
Blinding of participants and personnel (performance bias)	Low risk	Double blinded and double dummy. Placebo capsules provided for all patients to maintain blind design
Blinding of outcome assessment (detection bias)	Unclear risk	Double blind without additional details
Incomplete outcome data (attrition bias)	Low risk	Adequate information provided on withdrawals. Less than 20 percent withdrew from study.
Selective reporting (reporting bias)	Low risk	No protocol but outcomes in methods included in results
Other bias	High risk	Exploratory research design chosen, making it difficult to compare the outcomes of the various groups

(Drosos et al., 1998)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised without additional information
Allocation concealment (selection bias)	Low risk	Randomization tables used for allocation
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	Hand and wrist radiographs provided to each patient evaluated blindly using Larsen's system.
Incomplete outcome data (attrition bias)	Low risk	Adequate information on withdrawn participants. Withdrawal rates lower than 20 percent (only 7 out of 103). Group data balanced out despite withdrawals
Selective reporting (reporting bias)	Unclear risk	Protocol not available but usual outcomes reported

Other bias	Low risk	No other biases detected

(Toulmonde et al., 2019)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization without further details
Allocation concealment (selection bias)	Low risk	Centralized web-based randomization system. Stratified based on inclusion centre and tumour location. Minimization randomization used
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	Centrally blinded review of radiological data
Incomplete outcome data (attrition bias)	High risk	High proportion (over 20 percent) of withdrawal rates on basis of adverse effects
Selective reporting (reporting bias)	Low risk	Study protocol included. Usual outcomes reported.
Other bias	High risk	Study design non-comparative

(Van der Veen et al., 1996)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization without further details on method
Allocation concealment (selection bias)	Unclear risk	Randomization without further details
Blinding of participants and personnel (performance bias)	Low risk	Double blinded and placebo controlled. Use of blinded capsules containing either medications

Blinding of outcome assessment (detection bias)	Unclear risk	Double blinded with no further information
Incomplete outcome data (attrition bias)	High risk	High withdrawal rates (over 40 percent).
Selective reporting (reporting bias)	Unclear risk	No study protocol included
Other bias	Low risk	No other bias detected
(De Groot et al., 2005)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized with no further details
Allocation concealment (selection bias)	Low risk	Randomization carried out by blocks of four by country. Stratification by diagnosis.
Blinding of participants and personnel (performance bias)	High risk	Un-blinded
Blinding of outcome assessment (detection bias)	High risk	Un-blinded (open label)
Incomplete outcome data (attrition bias)	Low risk	Acceptable rates of dropout (less than 20 percent). Reasons for withdrawal provided.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes listed in methods match those included in results
Other bias	Low risk	No other detected bias

(Keystone, 2005)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized with no additional details

Allocation concealment (selection bias)	Unclear risk	Randomized without sufficient details
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinded with no further details
Blinding of outcome assessment (detection bias)	Unclear risk	Double blinded with no additional details
Incomplete outcome data (attrition bias)	Unclear risk	No proper reporting of incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol included. Outcomes in methods included in results
Other bias	Low risk	No other bias detected

(Smolen et al., 2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each of three groups were reported
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Van Rhee et al., 2014)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule and stratified by baseline concomitant corticosteroid use
Allocation concealment (selection bias)	Low risk	Concealment scheme described in 'Methods' section
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to allow judgment
Incomplete outcome data (attrition bias)	Unclear risk of bias	Insufficient reporting of attrition/exclusions to allow judgment
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other bias detected

(Aletaha et al., 2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization process is described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians

Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Khanna et al., 2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocations likely could not have been foreseen in before or during enrolment.
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study, Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Investigators, patients, and sponsor personnel were masked to treatment assignment. To prevent unmasking, separate assessors evaluated efficacy and safety.
Incomplete outcome data (attrition bias)	Low risk	The participants withdrew from the study due to various reasons. Summarised in table
Selective reporting (reporting bias)	Low risk	All outcomes in methods section were listed
Other bias	Low risk	No other bias detected

(Tanaka et al., 2019)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	The randomization sequence generation performed via an interactive voice or interactive web response system, with allocation stratified
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study, Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians the exception being for code-breaking if an adverse event (AE) occurred
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each groups were reported
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other bias detected

(Taylor et al., 2018)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described. But they state more details are on their online supplementary methods and result.
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.

Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Bingham et al., 2015)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was not mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	High risk	No participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	High risk	Patients were not assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Burmester et al., 2017a)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods section are reported
Other bias	Low risk	No other bias detected

(Burmester et al., 2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was not mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.

Selective reporting (reporting bias)	Low risk	Outcomes described in methods section are reported
Other bias	Low risk	No other bias detected

(Fleischmann et al., 2013)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Stud design involved both double blind treatment and open labelled groups.
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Some patients were assessed by blinded physicians others were not
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. The percentage from each of three groups were reported
Selective reporting (reporting bias)	Low risk	Outcomes in methods section were recorded in study results
Other bias	Low risk	No other bias detected

(Gabay et al., 2013)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomization sequence generation method was described

Allocation concealment (selection bias)	Low risk	The methods used to conceal the allocation sequence are not described but all involved in the study were masked
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Numbers were reported
Selective reporting (reporting bias)	Low risk	All outcomes are reported
Other bias	Low risk	No other bias detected

(Giles et al., 2020)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomization sequence generation method was mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	High risk	Open-label, parallel-group tri; Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Patients were not assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.

Selective reporting (reporting bias)	Low risk	All outcomes are reported
Other bias	Low risk	No other bias detected

(Yazici et al., 2012)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each of two groups were reported
Selective reporting (reporting bias)	Low risk	All outcomes highlighted in methods were discussed
Other bias	Low risk	No other bias detected

(Nasonov et al., 2020)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described

Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Unclear risk of bias	Some of the participants withdrew from the study due to various reasons. Number from each of two groups were reported
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Genovese et al., 2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The randomization scheme is not described in sufficient detail. The article only says "Patients were randomized in a 2:1 ratio to receive either tocilizumab or placebo combined with stable DMARD therapy"
Allocation concealment (selection bias)	Unclear risk	The article does not describe the method used to conceal the allocation sequence in sufficient detail. It only talks of the study being a double-blind study.
Blinding of participants and personnel (performance bias)	Unclear risk	The study does not describe all measures used, to blind study participants and personnel from knowledge of which intervention a participant received.

Blinding of outcome assessment (detection bias)	Low risk	The article describes blinding of outcome assessment in the statement "Patients were assessed using a dual-assessor approach for efficacy and safety evaluations, to ensure that blinding was not compromised."
Incomplete outcome data (attrition bias)	Low Risk	The article was clear on the interruption and stoppage of the study for those who attained certain parameters and even provided the numbers for those who left or ended up being excluded for both the study. This is adequately described in Figure 1 on page 2970.
Selective reporting (reporting bias)	Unclear risk	The article does not state how the possibility of selective outcome reporting was examined by the authors and what was found
Other bias	Low risk	No other bias detected

(Smolen et al., 2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each of three groups were reported
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting

Other bias	Low risk	No other bias detected

(Van Rhee et al., 2014)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule and stratified by baseline concomitant corticosteroid use
Allocation concealment (selection bias)	Low risk	Concealment scheme described in 'Methods' section
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to allow judgment
Incomplete outcome data (attrition bias)	Unclear risk of bias	Insufficient reporting of attrition/exclusions to allow judgment
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other bias detected

(Aletaha et al., 2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization process is described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded

Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Khanna et al., 2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocations likely could not have been foreseen in before or during enrolment.
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study, Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Investigators, patients, and sponsor personnel were masked to treatment assignment. To prevent unmasking, separate assessors evaluated efficacy and safety.
Incomplete outcome data (attrition bias)	Low risk	The participants withdrew from the study due to various reasons. Summarised in table
Selective reporting (reporting bias)	Low risk	All outcomes in methods section were listed
Other bias	Low risk	No other bias detected

(Tanaka et al., 2019)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	The randomization sequence generation performed via an interactive voice or interactive web response system, with allocation stratified
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study, Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians the exception being for code-breaking if an adverse event (AE) occurred
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each groups were reported
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other bias detected

(Taylor et al., 2018)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described. But they state more details are on their online supplementary methods and result.

Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Bingham et al., 2015)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was not mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	High risk	No participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	High risk	Patients were not assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Burmester et al., 2017a)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Low risk	Outcomes described in methods section are reported
Other bias	Low risk	No other bias detected

(Burmester et al., 2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was not mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.

Selective reporting (reporting bias)	Low risk	Outcomes described in methods section are reported
Other bias	Low risk	No other bias detected

(Fleischmann et al., 2013)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Unclear risk of bias	Stud design involved both double blind treatment and open labelled groups.
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Some patients were assessed by blinded physicians others were not
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. The percentage from each of three groups were reported
Selective reporting (reporting bias)	Low risk	Outcomes in methods section were recorded in study results
Other bias	Low risk	No other bias detected

(Gabay et al., 2013)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomization sequence generation method was described

Allocation concealment (selection bias)	Low risk	The methods used to conceal the allocation sequence are not described but all involved in the study were masked
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Numbers were reported
Selective reporting (reporting bias)	Low risk	All outcomes are reported
Other bias	Low risk	No other bias detected

(Giles et al., 2020)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomization sequence generation method was mentioned
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	High risk	Open-label, parallel-group tri; Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Patients were not assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons.
Selective reporting (reporting bias)	Low risk	All outcomes are reported
Other bias	Low risk	No other bias detected

(Yazici et al., 2012)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described
Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Low risk	Some of the participants withdrew from the study due to various reasons. Number from each of two groups were reported
Selective reporting (reporting bias)	Low risk	All outcomes highlighted in methods were discussed
Other bias	Low risk	No other bias detected

(Nasonov et al., 2020)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk of bias	The randomization sequence generation method was mentioned but not well described

Allocation concealment (selection bias)	Unclear risk of bias	The methods used to conceal the allocation sequence are not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind study; Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Patients were assessed by blinded physicians
Incomplete outcome data (attrition bias)	Unclear risk of bias	Some of the participants withdrew from the study due to various reasons. Number from each of two groups were reported
Selective reporting (reporting bias)	Unclear risk of bias	Insufficient information to highlight selective outcome reporting
Other bias	Low risk	No other bias detected

(Genovese et al., 2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The randomization scheme is not described in sufficient detail. The article only says "Patients were randomized in a 2:1 ratio to receive either tocilizumab or placebo combined with stable DMARD therapy"
Allocation concealment (selection bias)	Unclear risk	The article does not describe the method used to conceal the allocation sequence in sufficient detail. It only talks of the study being a double-blind study.
Blinding of participants and personnel (performance bias)	Unclear risk	The study does not describe all measures used, to blind study participants and personnel from knowledge of which intervention a participant received.
Blinding of outcome assessment (detection bias)	Low risk	The article describes blinding of outcome assessment in the statement "Patients were assessed using a dual-assessor approach for efficacy and safety evaluations, to ensure that blinding was not compromised."
Incomplete outcome data (attrition bias)	Low Risk	The article was clear on the interruption and stoppage of the study for those who attained

		certain parameters and even provided the numbers for those who left or ended up being excluded for both the study. This is adequately described in Figure 1 on page 2970.
Selective reporting (reporting bias)	Unclear risk	The article does not state how the possibility of selective outcome reporting was examined by the authors and what was found
Other bias	Low risk	No other bias detected

(Yunyun et al., 2019)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the selection centre
Allocation concealment (selection bias)	High Risk	No concealment done
Blinding of participants and personnel (performance bias)	High Risk	Participants and personnel not blinded
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment
Incomplete outcome data (attrition bias)	Low Risk	All study samples had their data evaluated and recorded accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	The information provided was not enough

(Vitko et al., 2006)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the selection centre

Allocation concealment (selection bias)	Unclear	Information not enough
Blinding of participants and personnel (performance bias)	Unclear	Information not clear
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment
Incomplete outcome data (attrition bias)	Low Risk	All study samples had their data evaluated and recorded accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	High Risk	The presence of 72 centers spread across 15 different nations increased the likelihood of bias

(Takahashi et al., 2013)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the selection centre
Allocation concealment (selection bias)	Unclear	Information not enough
Blinding of participants and personnel (performance bias)	Unclear	Information not clear
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment
Incomplete outcome data (attrition bias)	Low Risk	All study samples had their data evaluated and recorded accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Low risk	The information available is not enough to make a clear conclusion

(Sundel et al., 2012)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection
Allocation concealment (selection bias)	Low Risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear	The information provided is not enough to establish other bias

(Strand et al., 1999)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized study
Allocation concealment (selection bias)	Low Risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind, placebo, and active-controlled
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment

Incomplete outcome data (attrition bias)	Low Risk	All centres reported the data and documented it accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes listed reported
Other bias	High Risk	Forty-seven universities participated in the study, which significantly increased the possibility of other bias

(Sticherling et al., 2017)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection
Allocation concealment (selection bias)	High Risk	No concealment was done at any stage of the study
Blinding of participants and personnel (performance bias)	High Risk	Non-blinded clinical trial
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment done
Incomplete outcome data (attrition bias)	Low Risk	All centres reported and documented their data
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Low Risk	The study sample was relatively low at 64 patients which reduced the chances of other bias

(Smolen, 1999)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the hospital
Allocation concealment (selection bias)	Low Risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment was done
Incomplete outcome data (attrition bias)	Low Risk	All the study samples had their data collected and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	The data provided was not clear/enough to have a proper conclusion

(Tedesco-Silva et al., 2007)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the selection centres
Allocation concealment (selection bias)	Low Risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind assessment was done accordingly
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data recorded and documented

Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	High Risk	The presence of a high number of centres (47) in multiple countries increased the probability of other bias

(Schiff et al., 2010)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme generated at the selection centres
Allocation concealment (selection bias)	Low Risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind assessment was done accordingly
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Available data is not enough to provide a valid conclusion on other bias

(Najarian et al., 1985)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a clear conclusion

(Metzler et al., 2007)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly

Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Low Risk	The number of participants and centres was few which reduced significantly the probability of other bias

(Kremer et al., 2004)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Data not enough to support a conclusive finding of other bias

(Karanikolas et al., 2006)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a clear conclusion

(Kahan, 2000)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented

Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	High Risk	The number of participants was relatively large at 719 which increased the likelihood of other bias

(Kahaly et al., 2018)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Data not enough to support a conclusive finding of other bias

(Ishaq et al., 2011)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres

Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Data not enough to support a conclusive finding of other bias

(Ioannides et al., 2012)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	High Risk	No concealment was done at any stage
Blinding of participants and personnel (performance bias)	High Risk	Prospective non-blinded trial
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment done
Incomplete outcome data (attrition bias)	Low Risk	All centres reported their data accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Low Risk	The length of the study of about five years provides the researchers enough time to identify and deal with possible other bias

(Gheith et al., 2007)

Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a clear conclusion

(Emery et al., 2009)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented

Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Data not enough to support a conclusive finding of other bias

(De Simone et al., 2009)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a clear conclusion

(Boudjema et al., 2011)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	High Risk	No concealment was done at any stage
Blinding of participants and personnel (performance bias)	High Risk	Non-blind

Blinding of outcome assessment (detection bias)	High Risk	No assessment done
Incomplete outcome data (attrition bias)	Low Risk	All participants apart from one who died in the trial had their data recorded and documented accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes listed reported
Other bias	Low Risk	The number of centres and sample were relatively low reducing the likelihood of other bias

(Beissert et al., 2009)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized open-label trial
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a clear conclusion

(Becker et al., 2008)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	High Risk	About 30 percent of participants never completed the study and their data mot recorded and used
Selective reporting (reporting bias)	High Risk	Some of the reporting was not done effectively due to the withdrawal of some sample patients
Other bias	High Risk	The high number of withdrawing patients increased the likelihood of other bias

(Yamamoto et al., 2014b)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented

Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Unclear Risk	Data not enough to support a conclusive finding of other bias

(Westhovens et al., 2006)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	High Risk	The number of participants was relatively high which increased the likelihood of the occurrence of other bias

(van Vollenhoven et al., 2016)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial

Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All centres had their data reported and documented
Selective reporting (reporting bias)	Low Risk	All outcomes reported
Other bias	Low Risk	The number of participants was relatively small which reduced the likelihood of the occurrence of other bias

(van der Heijde et al., 2006)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High Risk	About 100 participants had their data unreported and documented
Selective reporting (reporting bias)	High Risk	The unreported participants negatively affected the reporting of their outcomes
Other bias	Unclear	The available data is not clear

(Takeuchi et al., 2021)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Unclear	No information provided
Blinding of participants and personnel (performance bias)	Unclear	No information provided
Blinding of outcome assessment (detection bias)	Unclear	No information provided
Incomplete outcome data (attrition bias)	High Risk	All of the participants never completed the study and their data was not recorded and used
Selective reporting (reporting bias)	High Risk	All outcomes not reported
Other bias	Unclear	Data is not enough to warrant a clear conclusion on the occurrence of other bias

(Smolen et al., 2009b)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment

Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The available data is not clear

(Sieper et al., 2013)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The number of centres spread across different nations increased the likelihood of other bias

(Schiff et al., 2014)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres

Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High Risk	About 36 percent of the participants had their data unreported and documented
Selective reporting (reporting bias)	High Risk	The unreported participants negatively affected the reporting of their outcomes
Other bias	Unclear	The available data is not clear

(Salvarani et al., 2007)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The information provided is not enough to make a credible conclusion on the other bias

(Hall III et al., 2015)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Low Risk	The study sample at 24 was relatively small, which reduced the probability of occurrence of other bias

(Regueiro et al., 2016)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed

Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The study sample and centres were relatively high at 104 spread across multiple nations which increased the probability of the occurrence of other bias

(Menter et al., 2007)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The study sample and centres were relatively high at 63 spread across North America and Europe which increased the probability of the occurrence of other bias

(Mease et al., 2005)		
Bias	**Authors' Judgement**	**Support for Judgement**

Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(McInnes et al., 2020)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported

Other bias	High Risk	The presence of a significant number of sites at 168 across 26 nations increased the probability of other bias

(Maini et al., 1999)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Landewé et al., 2014)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial

Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The presence of a significant number of sites at 83 across North America, South America, and Europe increased the probability of other bias

(Cai et al., 2017)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Keystone et al., 2008)		
Bias	**Authors' Judgement**	**Support for Judgement**

Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The number of participants was relatively high at over 900 which increased the probability of the occurrence of other bias

(Van de Kerkhof et al., 2008)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly

Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Kavanaugh et al., 2009)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low risk	Randomized centralized interactive voice response system selection
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Judson et al., 2015)		
Bias	**Authors' Judgement**	**Support for Judgement**

Random sequence generation (selection bias)	Low risk	Randomized scheme selection
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Low Risk	The presence of a small study sample reduced the probability of the occurrence of other bias

(Holgate et al., 2011)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low risk	Randomized scheme selection
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly

Other bias	Low Risk	The presence of a small study sample, as well as a short research period, reduced the probability of the occurrence of other bias

(Yamamoto et al., 2014a)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low risk	Randomized centralized interactive voice response system selection
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Grant et al., 2010)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized prospective clinical trial
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study

Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Gottlieb et al., 2003)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized prospective clinical trial
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All trial centres had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Unclear	The available information was not enough to identify the probability of the occurrence of other bias

(Weinblatt et al., 2013)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized prospective clinical trial
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All trial centre had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Low Risk	The study sample was relatively small as well as the research period, which reduced the probability of occurrence of other bias

(Beissert et al., 2010)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	High Risk	Some of participants never completed the study and their data mot recorded and used

Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	High Risk	The high number of withdrawing patients increased the likelihood of other bias

(Smolen et al., 2015)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized prospective clinical trial
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All the trial centres had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Low Risk	The length of the clinical trials was relatively long which reduced the probability of occurrence of other bias

(Emery et al., 2009)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized prospective clinical trial
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind study

Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed accordingly
Incomplete outcome data (attrition bias)	Low Risk	All the trial centres had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported accordingly
Other bias	Low Risk	The length of the clinical trials was relatively long with the initial study taking 52 weeks followed by an extension of 5 years which reduced the probability of occurrence of other bias

(Deodhar et al., 2019)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	High Risk	The presence of a significant number of centres at 80 across Australia, North America, Taiwan, and Europe increased the probability of other bias

(Combe et al., 2006)

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	High Risk	23 percent of the study sample never completed the study and their data documented
Selective reporting (reporting bias)	High Risk	All outcomes were not reported since not all selected samples completed the study
Other bias	Unclear	The information available was not enough to make a justified conclusion

(Butchart et al., 2015)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented

Selective reporting (reporting bias)	Low Risk	All outcomes were reported
Other bias	Unclear	The available information was not enough to make a sound conclusion on the availability of other bias

(Smolen et al., 2009a)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed accordingly
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes listed were reported
Other bias	Unclear	The available information was not enough to make a sound conclusion on the availability of other bias

(Anthony A. Amato and Richard Barohn, 2011)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of study sample
Allocation concealment (selection bias)	Low Risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low Risk	Double-blind clinical trial

Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome was assessed accordingly
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low Risk	All outcomes listed were reported
Other bias	Low Risk	The number of participants was relatively low at 16 which significantly reduced the likelihood of other bias

(Aitken et al., 2018)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized scheme selection
Allocation concealment (selection bias)	Low Risk	Concealment was done at the selection point
Blinding of participants and personnel (performance bias)	Low Risk	A double-blind placebo-controlled crossover trial
Blinding of outcome assessment (detection bias)	Low Risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low Risk	All participants had their data recorded and evaluated accordingly
Selective reporting (reporting bias)	Low Risk	All outcomes were recorded accordingly
Other bias	Low Risk	The number of participants was low at 51 and the research period low at 12 weeks which reduced the probability of occurrence of other bias

(Schiff et al., 2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly picked sample from 169 centres in 9 countries.
Allocation concealment (selection bias)	Low risk	The concealment scheme was implemented at the treatment centres.
Blinding of participants and personnel (performance bias)	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear	All centres had their data recorded and analyzed
Selective reporting (reporting bias)	Low risk	All the outcomes were reported
Other bias	Unclear	No other bias was recorded

(Sheng et al., 2020)		
Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomly picked sample
Allocation concealment (selection bias)	Low risk	Concealment at the treatment centres
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All the participants were evaluated

Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear	There is no sufficient information in this regard

(Pakfetrat et al., 2010)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly picked sample
Allocation concealment (selection bias)	Low risk	Done in the treatment centre
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Assessment done
Incomplete outcome data (attrition bias)	Low risk	All samples had their data recorded and reported
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear	Information is not enough to identify other bias

(Poiley et al., 2016)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sample selected from treatment centres
Allocation concealment (selection bias)	Low risk	Concealment done at the selection centre

Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	The blind outcome was assessed
Incomplete outcome data (attrition bias)	Low risk	All participants had their data recorded
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low	The use of electronic diary significantly reduced the presence of other bias

(Schlesinger et al., 2011)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly picked sample
Allocation concealment (selection bias)	Low risk	Concealment done at the clinical centre
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All participants were recorded and assessed
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Other bias	High	The sample is not a complete representation of all the patients required

(Terkeltaub et al., 2010)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sample was randomly selected
Allocation concealment (selection bias)	Low risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low risk	Double-blind assessment
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All the samples had their data recorded
Selective reporting (reporting bias)	Low risk	All the outcomes were reported
Other bias	Low risk	The use of non-a placebo-controlled design gave enough time to evaluate changes from baseline in quality of life, joint function, and physician global assessments.

(Tahir et al., 2017)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized sample selection
Allocation concealment (selection bias)	Low risk	Concealment done at selection centre

Blinding of participants and personnel (performance bias)	Low risk	Double-blind assessment
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Unclear	Some data from some samples were not considered in the final assessment
Selective reporting (reporting bias)	Unclear	The data from samples who escaped at week 16 incomplete
Other bias	Low	The data missing due to patients escaping at week 16 was handled as non-responders in order to minimize bias.

(Alten et al., 2011)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection from hospital data
Allocation concealment (selection bias)	Low risk	Concealment implemented in clinical trials
Blinding of participants and personnel (performance bias)	Low risk	Double-blind assessment
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All samples had their data recorded and assessed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High	The sample selected had to meet criteria that may have locked out potential participants

(Choudhury et al., 2016)

Bias	Authers' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomizes selection
Allocation concealment (selection bias)	Low risk	Concealment done at clinical centres
Blinding of participants and personnel (performance bias)	Low risk	Double-blind assessment
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All the centres had their data analyzed
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear	The sample was selected from centres in several nations, making it difficult to have a clear evaluation of other bias

(Ridker et al., 2012)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment done at selection centre
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment

Incomplete outcome data (attrition bias)	Low risk	All participants' data were well recorded and assessed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Criteria for selecting sample and reporting is clear

(Russell et al., 2019)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized sample selection
Allocation concealment (selection bias)	Low risk	Concealment done at the clinical trials
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessed
Incomplete outcome data (attrition bias)	Low risk	All samples were adequately reported and assessed
Selective reporting (reporting bias)	Low risk	The outcomes were effectively reported
Other bias	High	The sample comprised a relatively high number of males at 71%

(Rich et al., 2013)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized scheme from hospital records

Allocation concealment (selection bias)	Low risk	Concealment done at the clinical trials centres
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All centre were reported and documented
Selective reporting (reporting bias)	Low risk	Outcomes reported accordingly
Other bias	Unclear	The data is not clear to establish other bias

(Ryan et al., 2018)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment done at the clinical trials
Blinding of participants and personnel (performance bias)	Low risk	Participants blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome was assessed
Incomplete outcome data (attrition bias)	Low risk	All participants had their data collected and assessed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear	Data is not enough to assess the availability of other bias

(Pavelka et al., 2015)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment was done at the selection centers
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Blind assessment done
Incomplete outcome data (attrition bias)	Low risk	All centres reported their data accordingly
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	The number of centres was relatively large at 64 and spread across various nations, making it highly likely to have non-reported bias.

(Paul et al., 2019)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly selected participants
Allocation concealment (selection bias)	Low risk	The concealment was done at the clinical trails
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, head-to-head trial
Blinding of outcome assessment (detection bias)	Low risk	The blind outcome was assessed

Incomplete outcome data (attrition bias)	Low risk	All samples had their data reported and analysed
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	The period of study was long at 52 weeks which provided the opportunity to deal with most of the likely bias.

(Papp et al., 2014a)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection from hospital data
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Out of the 181 participants, only 144 completed the mandatory 120 weeks required
Selective reporting (reporting bias)	High risk	The unreported data by the participants who never completed the 120 weeks was not enough
Other bias	Unclear	Apart from those who never completed the 120 weeks, there is little information to make a valid conclusion

(Nash et al., 2017)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection of participants
Allocation concealment (selection bias)	Low risk	Concealment done at the clinical trial centres

Blinding of participants and personnel (performance bias)	Low risk	Double-blind, multicentre, randomized, placebo-controlled study
Blinding of outcome assessment (detection bias)	Low risk	Assessment was done
Incomplete outcome data (attrition bias)	Low risk	All centres reported their data and were documented accordingly
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	High risk	The number of centres was relatively high at 109 across various nations, increasing the likelihood of other bias.

(Mease et al., 2018)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment done
Incomplete outcome data (attrition bias)	Unclear	The data presented is not clear enough
Selective reporting (reporting bias)	Unclear	The data is not clear due to the high number of participants
Other bias	High risk	The number of participants was relatively high at over 900, increasing the possibility of other bias

(Langley et al., 2015)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection of participants
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All participants had their data recorded and well documented
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The participants were few and the research timeline was short reducing the probability of more bias

(Kivitz et al., 2018)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment done at clinical trials centres
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded

Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All centres reported and documented their data accordingly
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	The number of centres was high at 85 in 19 different nations significantly increasing the chances of other bias

(Paul et al., 2015)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Double-blind assessment
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment was done
Incomplete outcome data (attrition bias)	Low risk	All participants had their data collected, documented, and analysed
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	The data is not enough to give a sound conclusion

(Mease et al., 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment done
Incomplete outcome data (attrition bias)	Low risk	All participants were recorded and their data examined
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	The number of participants was relatively low as well as the study period

(Huang et al., 2020)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection scheme

Allocation concealment (selection bias)	Low risk	Concealment done at selection centre
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment done
Incomplete outcome data (attrition bias)	Low risk	All participants had their data recorded and documented
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study period was long averaging three years providing the researchers enough time to identify and deal with other possible bias

(Dokoupilová et al., 2018)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized scheme
Allocation concealment (selection bias)	Low risk	Concealment was done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Blind assessment done
Incomplete outcome data (attrition bias)	High risk	Some of the participants never completed the study meaning some data was not incorporated into the assessment
Selective reporting (reporting bias)	Low risk	All outcomes reported

Other bias	Unclear risk	The data provided is not enough to make a proper judgment

(Deodhar et al., 2021)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection of participants
Allocation concealment (selection bias)	Low risk	Double-blind
Blinding of participants and personnel (performance bias)	Low risk	Double-blind placebo-controlled study
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All the selected participants had their data recorded and assessed accordingly
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Very high	The participants self-administered the medicine through syringes which leaves an opportunity for other bias

(Braun et al., 2017)		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomized selection
Allocation concealment (selection bias)	Low risk	The concealment scheme was implemented during the selection and assessment stages
Blinding of participants and personnel (performance bias)	Low risk	blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind assessment done
Incomplete outcome data (attrition bias)	Low risk	All participants had their data recorded and analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Data was not enough to support a competent evaluation

(Bagel et al., 2021)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection scheme
Allocation concealment (selection bias)	Low risk	Concealment done at the selection stage
Blinding of participants and personnel (performance bias)	Low risk	Double-blind parallel-group
Blinding of outcome assessment (detection bias)	Low risk	Blind assessment done accordingly
Incomplete outcome data (attrition bias)	Low risk	All participants were well documented and assessed

Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear	Data is not enough to support a proper evaluation

(Papp et al., 2013)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized selection scheme
Allocation concealment (selection bias)	Low risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	Low risk	Double-blind placebo-controlled
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	All centres reported and recorded their data accordingly
Selective reporting (reporting bias)	Low risk	All outcomes were recorded
Other bias	High risk	The study comprised 19 centres in 6 nations which increased the chances of other biased

(Behrens et al., 2022)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized selection
Allocation concealment (selection bias)	Low risk	The concealment scheme was implemented during the selection and assessment stages

Blinding of participants and personnel (performance bias)	Low risk	blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind assessment done
Incomplete outcome data (attrition bias)	Low risk	All participants had their data recorded and analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Data was not enough to support a competent evaluation

(Belani et al., 2022)		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Randomized selection of sample
Allocation concealment (selection bias)	Low risk	Concealment done at the selection centre
Blinding of participants and personnel (performance bias)	High risk	Non-blinded clinical trial
Blinding of outcome assessment (detection bias)	High Risk	No blind assessment done
Incomplete outcome data (attrition bias)	Low Risk	All centres reported their data accordingly
Selective reporting (reporting bias)	Unclear	Not all outcomes reported
Other bias	Unclear	Data is not enough to support a proper evaluation

Appendix D: Funnel plots showing comparisons for Immunosuppressants drugs versus Placebo Or Active drugs

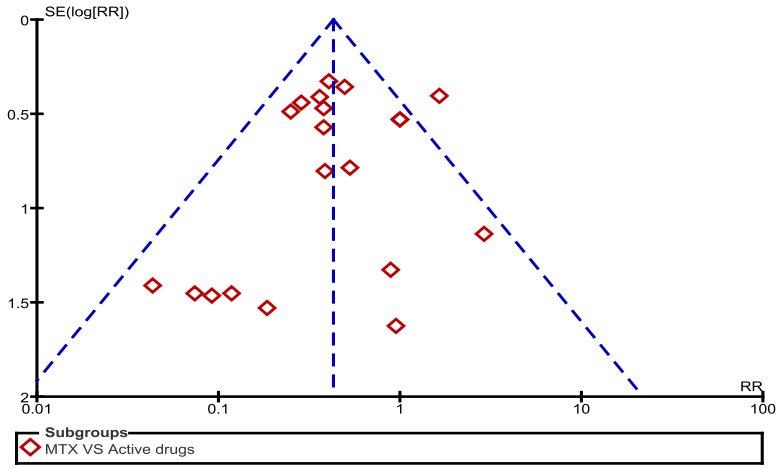

Figure D-1 : Methotrexate vs. Placebo or active on risk of hypertension

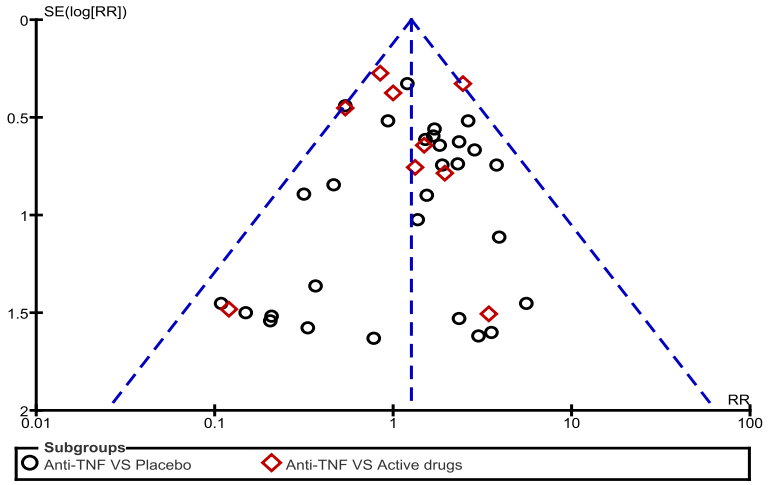

Figure D-2 : Anti-TNF vs. Placebo or active on risk of hypertension

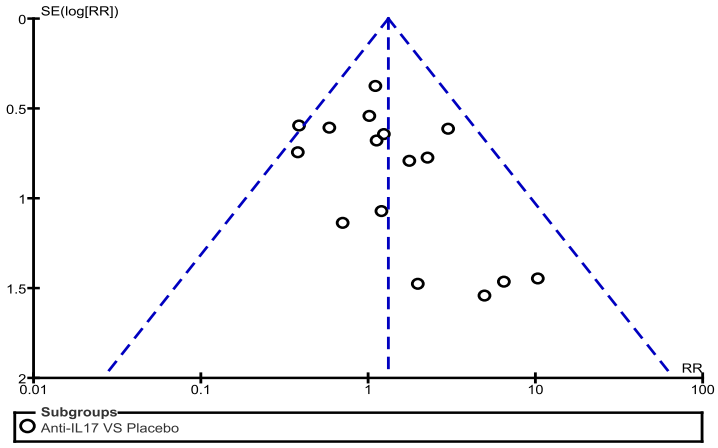

Figure D-3 : Anti-IL 17 vs. Placebo on risk of hypertension

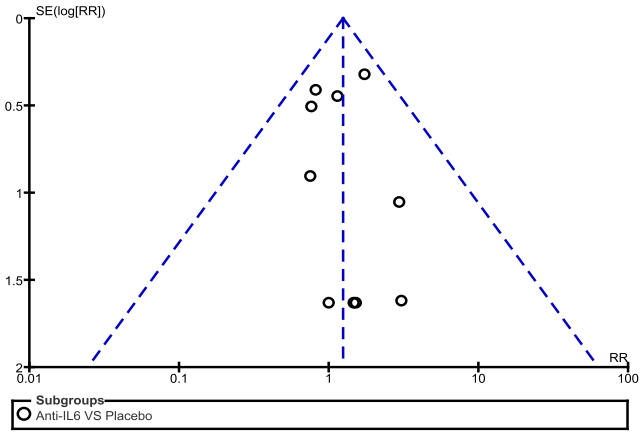

Figure D - 4 : Anti-IL6 vs. Placebo on risk of hypertension

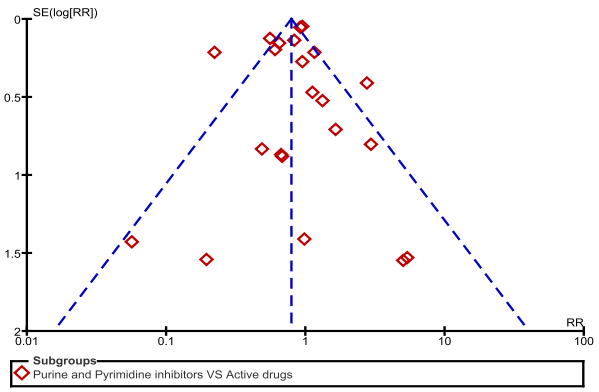

Figure D-5 : Purine and Pyrimidine synthesis inhibitors vs. Active on risk of hypertension

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