Guideline Directed Medical Therapy for Secondary Prevention after Coronary Artery Bypass Grafting

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Abstract

Atherosclerotic cardiovascular disease, and specifically coronary artery disease is a major cause of mortality and morbidity in the Unites States. A large proportion of patients with atherosclerotic cardiovascular disease receive coronary artery bypass grafting. However, despite this surgical intervention, patients are at continued risk for progression of atherosclerosis, both in their native coronary arteries as well as the conduits used for the coronary artery bypass surgery. Patients also have other cardiovascular risk factors, specifically diabetes, obesity, and many have poly-vascular disease. The American Heart Association has recommendations for pharmacotherapy in these patients, which is termed as guideline directed medical therapy for secondary prevention of cardiovascular disease.

The US Department of Veteran Affairs is the single largest unified healthcare system in the United States and supports the healthcare needs of approximately 9 million US Veterans. These people are older, more frail, and have more cardiovascular risk factors than the average US population. All these conditions put them at higher risk for recurrent cardiovascular events after receiving coronary artery bypass surgery.

Therefore, the overarching aim of my PhD was to study the use of guideline directed medical therapy and factors associated with non-use among US Veterans. To achieve this aim, six papers were completed and included in this thesis. The broad synopsis of the thesis is that guideline directed medical therapy does improve cardiovascular outcomes. However, the present use of these therapies among US Veterans is suboptimal; additionally, some reasons for non-use were identified. Therefore, in conclusion, more work needs to be done to ensure improved use of these life-saving therapies.

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Preface

I am enrolled in the PhD programme at the School of Health and Wellbeing, University of Glasgow, UK between 2021 till date. My PhD work was done as a part-time student along with clinical responsibilities as a staff cardiovascular surgeon at the Louis Stokes Cleveland VA Medical Centre and an Associate Professor of Surgery at the Case Western Reserve University, Cleveland, Ohio. The following is a brief outline of my clinical and scholarly work during this period.

Manuscripts included in this thesis

***Deo SV*,** Al-Kindi S, Motairek I, McAllister D, Shah ASV, Elgudin YE, Gorodeski EZ, Virani S, Petrie MC, Rajagopalan S, Sattar N. Impact of Residential Social Deprivation on Prediction of Heart Failure in Patients With Type 2 Diabetes: External Validation and Recalibration of the WATCH-DM Score Using Real World Data. Circ Cardiovasc Qual Outcomes. 2024 Mar;17(3):e010166. doi: 10.1161/CIRCOUTCOMES.123.010166. Epub 2024 Feb 8. PMID: 38328913; PMCID: PMC11093755.

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Other selected manuscripts published during the PhD period

This is a list of peer-reviewed manuscripts published during the PhD period where I am listed as the first or corresponding author (either sole or joint)

***Deo SV*,** Al-Kindi S, Salerno PRVO, Cotton A, Elgudin Y, Virani SS, Nasir K, Petrie MC, Sattar N, Rajagopalan S. Bayesian Model Projecting Cardiovascular Disease Related Mortality Trends in the United States. J Am Heart Assoc. 2024 Nov 5;13(21):e035922. doi: 10.1161/JAHA.124.035922. Epub 2024 Oct 25. PMID: 39450748; PMCID: PMC11935689.

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Journal Responsibilities

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The Lancet Regional Health: Europe
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Kerwin Cayton (MSc Epidemiology, Kent State U)
Katrina Terry (MSc Epidemiology, Kent State U)
Andrea Zelko (MSc Epidemiology, Kent State U)

Clinical Work

Adult Cardiac Surgery
Organ procurement for heart and lung transplantation

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My wife Vaishali; whatever I have achieved in the past decades is largely because of her love and sacrifice; it is difficult to express my gratitude in words.

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Author's Declaration

I declare that this thesis is the result of my own work. Published work of others have been cited where used. The papers presented in each chapter have been published in peer-reviewed journals. The manuscript included in each chapter is exactly as published in the journal; the only change to the published version is that the figures have been placed inside the manuscript at the location that they are cited, and tables have been placed in an appendix at the end of each chapter. This has been done to fulfil the University of Glasgow guidelines on preparation of a thesis by 'alternate' format.

The contents of this thesis have not been submitted for any other degree at the University of Glasgow or any other Institution.

Salil Vasudeo Deo MD

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Definitions/Abbreviations

This is a list of non-standard abbreviations included in the thesis. The non-standard abbreviations for each manuscript are provided at the beginning of each the manuscript in each chapter.

ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Disease in Diabetes
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
BIRLS	Beneficiary Identification Records Locator Subsystem
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CeVD	Cerebrovascular disease
CI	Confidence interval
CKD	Chronic Kidney disease
CPT	Common procedure terminology
EuroSCORE	European system for cardiac operative risk evaluation
GDMT	Guideline Directed Medical Therapy
GLP1-RA	Glucagon like peptide-1 receptor agonist
GND test	Greenwood Nam D'Agostino test
HbA1c	Glycosylated Haemoglobin
HDL	high density lipoprotein
HFrEF	Heart failure with reduction ejection fraction
hs-CRP	High sensitivity C-reactive protein
ICD	International classification of diseases
LDL-C	Low density lipoprotein type C
LLT	Lipid lowering therapy
LVEF	Left ventricular ejection fraction
MACE	Major Adverse Cardiovascular Events
MDR	VA Mortality Data Repository
MOR	Median Odds ratio
MRA	Mineralocorticoid receptor antagonist
NST	Non-statin therapy
O/E ratio	Observed/Expected ratio
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous intervention
PCSK9i	Proprotein convertase subtilsin/kexin type 9 inhibitors
PREVENT	Predicting risk of Cardiovascular Events
RAASi	Renin-angiotensin-aldosterone system inhibitor
RECODe	Risk Equations for Complicatons of type 2 Diabetes
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction
SD	Standardised Difference
SDI	Social Deprivation Index
SDoH	Social Determinants of Health

SGLT2i	Sodium Glucose Cotransporter-2 inhibitor
SMART2	the Secondary Manifestations of ARTerial disease
STS	Society of Thoracic Surgeons
T2D or T2DM	Type 2 diabetes
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
TRS-HF_{DM}	Thrombolysis in Myocardial Infarction) Risk Score for Heart Failure in Diabetes
VA	Department of Veterans Affairs
VA-PROM	VA Projected risk of mortality score
VASQIP	VA Surgical Initiative Project
VHR	Very high risk

Chapter 1 Defining the Problem

1 Introduction

1.1 Motivation

Burden of Cardiovascular Disease in the United States

Cardiovascular disease (CVD) is among the most common causes of mortality in the United States; in 2016, a Global Burden of Disease study reported that more than 900 000 deaths in the US were attributed to cardiovascular disease (Mensah et al., 2023). In August 2024, the Office of Health Policy provided the US Congress with an updated report outlining the burden of CVD in the US (Services and Evaluation, 2024). They reported that one-fifth of all adult Americans suffered from coronary artery disease (CAD); this prevalence rose to over 42% in all Medicare beneficiaries, namely adults aged 65 years or older. However, apart from a higher risk of mortality, CAD also confers an economic burden on the individual and the society at the population health level. In the US, CVD and stroke treatment accounted for $ 251 billion in healthcare spending in 2019 (Kazi et al., 2024). Analyzing data from a large healthcare system in California, in 2010, Nichols et al. reported that the mean direct annual cost per person of CVD treatment in the US was $ 18,953 (Nichols et al., 2010). To put that into perspective, as per data from the American Communities Survey, this is a little less than half of the median household income in the US (Bureau, 2025). Hence CVD treatment cost in the US is very expensive for patients. While all patients with CAD deserve appropriate medical therapy, a proportion of patients with advanced symptoms or critical anatomy need a ‘mechanical’ fix, either in the form of percutaneous intervention (PCI) or coronary artery bypass grafting (CABG). CABG recently celebrated its 50th decade since inception and it is currently among the most common adult cardiac surgical procedures performed in the US (Ghandakly et al., 2024). While patients with limited CAD may be treated with PCI, the presence of left main coronary artery stenosis, complex multi-vessel disease and preexisting type 2 diabetes (T2D) are all class I indications for CABG according to the American College of Cardiology/American Heart Association (Writing Committee et al., 2023). A recent study reported that the rate of CABG in developed countries was approximately 36.7 per 100,000

population (Vervoort et al., 2024). According to the Society of Thoracic Surgeons annual report, in 2019, 161,816 isolated CABG procedures were performed in the United States (Kim et al., 2023). Additionally, a multi-year national analysis of US data reported that overall annual CABG volume has remained constant in the United States (Raza et al., 2019). Hence, a substantial number of CAD patients in the United States undergo CABG annually.

Contemporary CABG outcomes

A pooled meta-analysis of six randomized trials that compared outcomes between percutaneous coronary intervention (PCI) and CABG over a median follow-up of 4.1 years reported that the long-term all-cause mortality was significantly lower following CABG compared to PCI [Risk ratio 0.73 [95% CI, 0.62-0.86] (Sipahi et al., 2014). In this study, CABG also had a lower risk for myocardial infarction and repeat coronary revascularization during follow-up. The Surgical Treatment for Ischemic Heart Failure (STICH) trial was a landmark trial that evaluated the clinical outcomes of 2121 patients with multi-vessel CAD and left ventricular dysfunction (defined as left ventricular ejection fraction <35%) randomized to receive optimal medical therapy or CABG. Over the 5-year follow-up period, compared to optimal medical therapy, patients who underwent CABG had significantly lower rates of heart failure hospitalization and cardiovascular mortality (Velazquez et al., 2011). In a meta-analysis that pooled patient-level data from 10 randomized trials, study investigators evaluated the clinical outcomes of patients with chronic kidney disease that were randomized to receive PCI or CABG. While overall mortality rates were comparable between CABG and PCI, patients who underwent CABG experienced lower rates of myocardial infarction and repeat coronary revascularization (Charytan et al., 2016). Thus, specific sub-groups of patients, particularly those with multi-vessel or left main stem disease, T2D, heart failure, or low left ventricular ejection fraction benefit from CABG rather than PCI or solely receiving medical therapy. Additionally, continuous improvements in surgical techniques, cardiopulmonary bypass technology, peri-operative care, and pre-operative patient optimization have all led towards reducing the risk-adjusted in-hospital mortality following CABG from 2.8% in 2003 to 1.7% in 2016 (Alkhouli et al., 2020). In fact, in the US, despite an increase in the pre-operative risk profile, the short-term (30-day)

mortality rate for CABG has reduced over the past three decades (Alkhouli et al., 2020) (Raza et al., 2019). However, although post-operative mortality has declined, patients continue to be at risk of experiencing major adverse cardiovascular events (MACE) following CABG specifically, myocardial infarction, stroke or the need for repeat coronary revascularization.

Need for guideline directed medical therapy post-CABG

As in all ASCVD patients, the atherosclerotic process can continue in the native coronary arteries post-CABG. However, post-CABG patients are additionally also susceptible to developing atherosclerosis in their coronary artery grafts. Arterial (the internal thoracic artery or radial artery) or venous conduits (greater saphenous vein) from the patient are used for coronary bypass at the time of CABG. Compared to the arterial conduit, saphenous vein grafts are more susceptible to developing atherosclerosis (Gharibeh et al., 2021). Differences between arteries and veins in vascular smooth muscle properties, biochemical composition, mechanical properties, and endothelial function are some reasons that may contribute towards this observed difference. However, the most recent Society of Thoracic Surgeons report investigated conduit use among all CABG procedures in the US and found that 90% of patients receive at least one saphenous vein graft (Bowdish et al., 2021). Hence, the optimal use of guideline directed medical therapy (GDMT) as secondary prevention post-CABG is very important in most patients to reduce the risk of ASCVD development and progression.

Benefit of secondary preventive therapy post-CABG

An observational study comprising 30 952 post-CABG patients reported that the use of a statin (hazard ratio (HR) 0.56), a renin-angiotensin-aldosterone-system inhibitor (RAASi) (HR 0.78), or an anti-platelet agent (HR 0.74) was associated with reduced risk for mortality over a 5 year median follow-up period (Bjorklund et al., 2020). A post-hoc analysis of the STICH trial that studied patients with ischemic cardiomyopathy reported that post-CABG patients receiving appropriate secondary preventive therapy (defined as the prescription of a statin plus an anti-platelet agent plus a RAASi) had significantly lower five-year

mortality rates than those not receiving such therapy (Wolfe et al., 2021). Researchers in Italy conducted a very interesting study where patients were prospectively enrolled in a comprehensive secondary preventive therapy arm and matched 1:1 to historical control patients in a retrospective manner. Over a minimum 1-year follow-up, compared to the historical control patients, those in the comprehensive secondary preventive therapy arm had a 59% lower risk of MACE. A pooled meta-analysis of 10 studies reported that good adherence to guideline directed medical therapy that included beta-blockers, renin-angiotensin-aldosterone-system antagonists, anti-platelet agents and statins resulted in lower all-cause mortality risk [risk ratio (RR) 0.56, 95% confidence interval (CI): 0.45, 0.69], cardiovascular mortality [RR 0.66, 95% CI: 0.51, 0.87] and cardiovascular hospitalization/myocardial infarction [RR 0.61, 95% CI: 0.45, 0.82]. Hence, there is overwhelming evidence that GDMT use as secondary prevention post-CABG reduces the long-term MACE risk and improves long-term survival.

1.2 Data Source

Background of the Data

The data used for all the manuscripts included in my thesis was sourced from the US Department of Veterans Affairs (VA). The current VA was originally established by President Abraham Lincoln in 1865 to take care of retired soldiers who fought in the Civil War. This single facility was gradually replaced by a unified healthcare system and became a cabinet level organization in 1988. Currently, the VA manages 150 hospitals, 800 outpatient community care clinics and supports the healthcare needs of approximately 9 million US Veterans at any given time.

Overview of the Data repository

The VA data is sourced from electronic health records information and supported by a dedicated team of data managers.

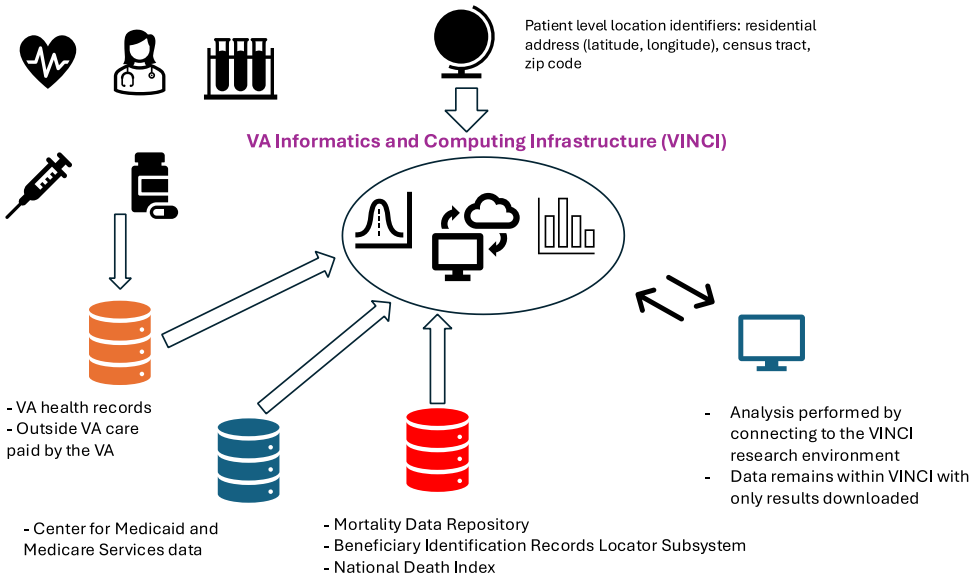


Figure 1-1 Diagrammatic representation of the VA data repository

Data from the VA electronic health records, other sources and vital status information is pooled into the VINCI. Analysis is performed in the trusted research environment of VINCI and results are downloaded onto the user's desktop.

Figure 1-1 provides a diagrammatic representation of the structure of the VA data repository which is called the VA Informatics and Computing infrastructure (VINCI). Data managers collect information from the electronic health records of all US Veterans and format this into multiple relational databases. There are separate databases for patient demographics, inpatient and outpatient health information, investigation results, laboratory test results, and pharmacy data. The Center for Medicare and Medicaid services, a federal agency that can provide health coverage to all US residents aged 65 years and above, also provides data on US Veterans enrolled with them. Vital status information is obtained from the Mortality Data Repository, the National Death Index and the Beneficiary Identification Records Locator Subsystem. The VA data managers ensure data accuracy and quality and update the vital status data each quarter. For my studies that used the information on patients who underwent CABG, the VA Surgical Quality Initiative Program (VASQIP) was my primary data source. The Continuous Improvement in Cardiac Surgery Program (CICSP) is an ongoing initiative started by the VA in 2009 and contains pre-operative, operative and post-operative information for all US Veterans that receive cardiac surgery at any of the VA medical centers that have a cardiac surgery programme. The VINCI

also contains accurate geolocation for each US Veteran's residential address that is recorded at the time of their inpatient or outpatient visit. New geolocation tables are created each year with updated information for all patients actively enrolled in VA care. Scrambled social security numbers are created as patient identifiers and are assigned to each US Veteran so that their information can be linked across the relational databases and also longitudinally tracked over time. For my studies, I accessed the data via the Microsoft Structure Query Language (SQL) Server interface and used SQL coding to identify patients, create my cohort of interest and link data across databases. I primarily used R 4.0.0 for Windows and STATA 16th edition for the statistical analyses and creating graphs and figures.

Thesis Overview

Considering the importance of GDMT use as secondary prevention in ASCVD patients, specifically for those that have received CABG surgery, and the limited information on this subject, I attempted to fill some gaps in the existing literature by studying this topic among US Veterans. In this thesis, I have tried to report some information regarding the current use of GDMT post-CABG, identify factors that may influence GDMT use, and evaluate risk prediction models that may assist in improving GDMT use as secondary prevention.

Structure of the Thesis: Paper connection

My thesis is an 'alternative' format thesis, i.e., each chapter included in the thesis is an original manuscript that has already been published in a peer-reviewed journal as follows: **Chapter 2, paper 1**: "*Trends in Prescriptions of Cardioprotective Diabetic Agents After Coronary Artery Bypass Grafting Among U.S. Veterans*" published in Diabetes Care, **Chapter 3, paper 2**: "*Disparities in PCSK9i Initiation Among US Veterans with Peripheral Arterial Disease or Cerebrovascular Disease*" published in the American. Journal of Cardiovascular Drugs, **chapter 4, paper 3**: "*Lipid-lowering in 'very high risk' patients undergoing coronary artery bypass surgery and its projected reduction in risk for recurrent vascular events - A Monte Carlo stepwise simulation approach*" published in the Journal of Cardiovascular Pharmacology, **chapter 5, paper 4**:

"*Validating the SMART2 score in a racially diverse high-risk nationwide cohort of patients receiving coronary artery bypass grafting*" published in the Journal of the American Heart Association, **chapter 6, paper 5**: "*The impact of residential social deprivation on prediction of heart failure in patients with type 2 diabetes mellitus: External validation and recalibration of the WATCH-DM score using real world data*" published in Circulation: Cardiovascular Quality and Outcomes, and **chapter 7, paper 6**: "*The time-varying cardiovascular benefits of glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus: Evidence from large multinational trials*" published in Diabetes, Obesity, and Metabolism.

Each chapter has a preface that explains how the paper presented in this chapter links to that in the prior one. All the papers presented in each chapter are exactly as published in their peer-reviewed journals. As per the 'alternative' format guidelines of the University the only changes made to the manuscript are: (i) figures (presented in both the main manuscript and the supplemental section) are placed where they are cited, (ii) tables (presented in both the main manuscript and the supplemental section) are placed at the end of the manuscript. Additionally, table numbering may vary from the published chapter as both main and supplemental tables were combined and presented together in the appendix of the chapter and they were numbered in order as per the text and, and (iii) citations are presented in the Harvard format and citations for the entire thesis are presented at the end.

The last chapter briefly presents my viewpoint regarding the dire need to improve GDMT use in ASCVD patients, my possible areas of future research, and the main skills and lessons learnt during this PhD process.

Chapter 2: Paper 1

2 Trends in prescriptions of cardioprotective diabetes agents after coronary artery bypass grafting among Veterans

2.1 Preface

Chapter 1 provided an overview of the guideline directed medical therapy recommendations for secondary prevention after coronary artery bypass grafting. As reported in the prior chapter, compliance with guideline directed medical therapy after CABG is poor (Pinho-Gomes et al., 2018). Additionally, Pinho-Gomes et al observed that the use of a combination of anti-platelet agents, beta-blockers and angiotensin converting enzyme inhibitors was consistently lower in those that received CABG rather than percutaneous coronary intervention, a difference that was consistent across the five-year trial period. Data from a more recent study, the 'Ticagrelor in CABG' trial (TICAB) reported that during the first year after CABG only 54% received guideline directed medical therapy, defined as a combination of an anti-platelet agent, statin, and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (Heer et al., 2022). Real-world data from post-CABG patients in Sweden reported higher yet suboptimal rates of medication use; while most patients received guideline directed medical therapy at discharge, at the end of the 8-year study period, the adherence rate for statins, beta-blockers, anti-platelet agents or renin-angiotensin aldosterone system inhibitors was only 60-80% (Bjorklund et al., 2020). In my review of the literature, I observed that, firstly, studies evaluating the use of guideline directed medical therapy after coronary artery bypass grafting are very few and, secondly, none studied recently introduced cardio-protective therapies (Bjorklund et al., 2020, Dimitriadis et al., 2021, Gao et al., 2017, Pan et al., 2022). Glucagon like peptide receptor agonists (GLP1-RA) and sodium glucose co-transporter inhibitors (sGLT2 inhibitors) are recently introduced cardio-protective medications (Commitee, 2025). Both these medications have demonstrated a cardio-protective effect in clinical trials and the 2024 Standard of Care Statement from the American

Diabetes Association recommends that all patients with atherosclerotic cardiovascular disease receive one or other drug (Commitee, 2025).

Hence, in this next paper, I evaluated the rate of GLP1-RA or SGLT2i initiation after CABG among US Veterans. I studied a nationwide cohort of US Veterans with T2D that underwent coronary artery bypass grafting across 41 VA medical centres from 2016 through 2019 and identified patients that were initiated on either agent within 6 months of their surgery date. I then fitted regression models to identify which patients were more likely to receive either medication.

2.2 Published Manuscript

Citation

Trends in Prescriptions of Cardioprotective Diabetic Agents After Coronary Artery Bypass Grafting Among U.S. Veterans.
Deo SV, McAllister DA, Al-Kindi S, Elgudin Y, Chu D, Pell J, Sattar N.Diabetes Care. 2022 Dec 1;45(12):3054-3057. doi: 10.2337/dc22-0570.PMID: 36256925

Manuscript

ABSTRACT

Introduction: Patients with type 2 diabetes mellitus (T2DM) undergoing coronary artery bypass grafting (CABG) are at risk of cardiovascular events. SGLT2i and GLP-1RA are effective cardio-protective agents, however, their prescription among CABG patients is uncertain.

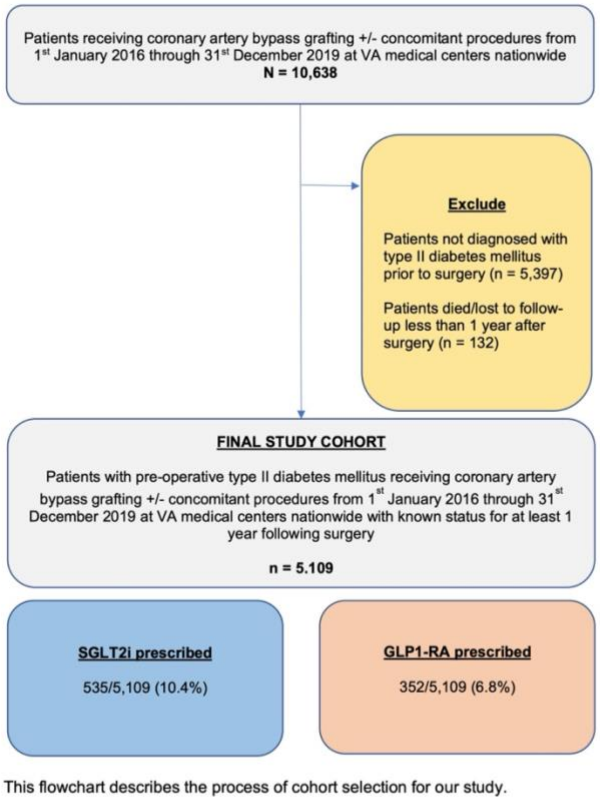
Methods: We analysed the nationwide Veteran Affairs database (2016 – 2019) to report trends and factors associated with SGLT2i or GLP1RA prescription after CABG.

Results: Among 5,109 patients operated at 40 different VA medical centres, 525/5109 (10.4%), 352/5109 (6.8%) and 91/5109 (1.8%) were prescribed SGLT2i, GLP-1RA and both respectively. Substantial increase in the quarterly SGLPT2i prescription rates (1.6% (2016Q1), 33% (2019Q4)) was present; less so for GLP-

1RA (0.8% (2016Q1), 11.2% (2019Q4)). SGLT2i use was less likely with pre-existing vascular disease (OR 0.75) or kidney disease (OR 0.72), while GLP-1RA use was associated with obesity (OR 1.91).

Conclusion: The overall utilization of SGLT2i or GLP-1RA drugs in US Veterans with T2DM undergoing CABG is low, with SGLT2i preferred over GLP-1RA.

INTRODUCTION



This flowchart describes the process of cohort selection for our study.

Figure 2-1. This flowchart outlines the process of cohort selection for our study

Coronary artery bypass grafting (CABG) is the preferred treatment for patients with type 2 diabetes mellitus (T2DM) and multivessel coronary artery disease (CAD) (Farkouh et al., 2012, d'Entremont et al., 2022). Sodium glucose cotransporter 2 receptor inhibitors (SGLT2i) and glucagon like peptide 1 receptor agonists (GLP-1RA) reduce cardiovascular risk in patients with T2DM and are, therefore, recommended for all T2DM patients with atherosclerotic vascular disease (ASCVD)(Cosentino et al., 2020) (Das et al., 2018). However, their adoption post CABG is uncertain. We, therefore, analysed patterns and trends for SGLT2i/GLP-1RA prescription in patients receiving CABG at Veterans Affairs (VA) medical centres nationwide. We evaluated longitudinal trends in SGLT2i / GLP-1RA use during the first post-operative year and studied clinical and socio-

economic factors associated with the use of these cardio-protective medications.

DESIGN AND METHODS

Our aims in this study were (i) to evaluate the overall use of SGLT2i / GLP-1RA after CABG and explore longitudinal trends, and (ii) examine patient related factors associated with the use of SGLT2i or GLP-1RA.

Study cohort: We analysed patients with T2DM that underwent CABG (1st January 2016 through 31st December 2019) at VA medical centres nationwide. We excluded patients with unknown vital status during the first post-operative year and used outpatient pharmacy fill records to determine patients that filled prescriptions for either a SGLT2i (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) or a GLP-1RA (Semaglutide, liraglutide, exenatide, dulaglutide). We obtained the pre-operative clinical, laboratory and socio-economic characteristics (community deprivation index, zip code derived median household income) for all patients (Figure 2-1).

Statistical analysis: We present data as counts (percentages) or medians (interquartile range (IQR)). We calculated proportions (with 95% confidence intervals (CI)) for SGLT2i and GLP-1RA use (i) for the entire study period (ii) for every quarter year (Q) and (iii) for each VA medical centre. We compared the use of SGLT2i and GLP-1RA for each VA medical centre using a correlation test. To study the association between baseline characteristics and SGLT2i/GLP-1RA use, we fit a multi-variable binomial logistic regression model with patient demographics (age, sex, race, ethnicity), clinical characteristics (heart failure (HF), heart failure with reduced ejection fraction (HFrEF), peripheral arterial disease (PAD), cerebrovascular disease, chronic kidney disease (CKD) etc), and socioeconomic data (community deprivation index, zip-code derived median household income) as covariates and SGLT2i or GLP-1RA use as the endpoint (Table 2-1). We report results as adjusted odds ratio (OR (95% CI)). To evaluate whether prescription rates for SGLT2i and GLP-1RA changed over time, we initially fit separate generalized additive model (GAM) of the quarterly prescription rates for each drug against time. On observing a substantial non-

linear increase in SGLT2i prescription rates over time, we performed a breakpoint analysis to identify that timepoint beyond which prescription rates increased.

Results: From 2016 - 2019, 5,109 patients with T2DM underwent CABG (median age 68 (IQR: 63, 71) years, 98.6 % male, 77.8% white, 11.6% Hispanic) at 40 VA medical centres. CKD, PAD, heart failure with reduced ejection fraction, and cerebrovascular disease were present in 38.6%, 27.9%, 9% and 6.8%, respectively (Table 2-2). Overall, 10.4% (95% CI: 9.6, 11.4) [535/5,109] and 6.8% (95% CI: 6.2, 7.6) [352/5,109] received a prescription for SGLT2i and GLP-1RA, respectively, and 1.8% (95% CI: 1.5, 2.2) [94/5,109] received both (Table 2-3). Variation in prescription rates between VA medical centres was large, with poor correlation between SGLT2i and GLP-1RA prescription rates in each VA medical centre (correlation coefficient: 0.08) (Figure 2-2, Figure 2-3).

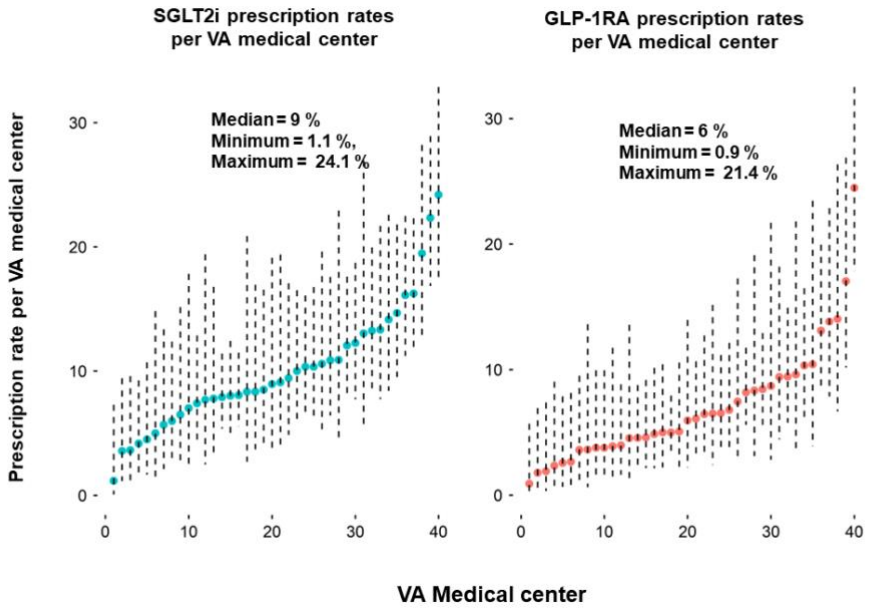


Figure 2-2. SGLT2i and GLP1-RA prescription rates for each VA medical centre

These two panels report the prescriptions rates observed over the study period for each VA medical centre. As demonstrated, there is substantial variation between centres.

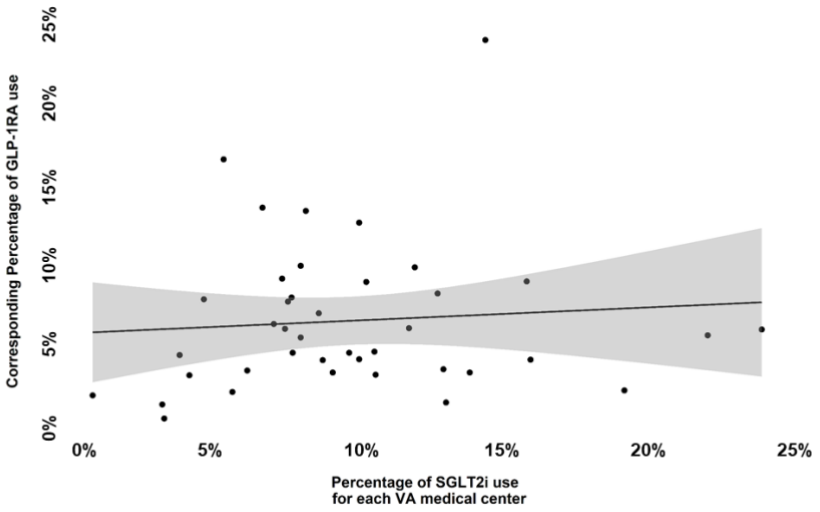


Figure 2-3. Correlation between SGLT2i and GLP1-RA use in VA medical centres

This scatterplot with fitted line demonstrates that there is very poor correlation between the SGLT2i and GLP1-RA prescription rates for each VA medical centre.

Patients with a higher median income [OR 1.08(1.03, 1.13) per 5,000 USD increase in median income], living in less deprived neighbourhoods [OR 1.19 (0.98, 1.44)] and patients with obesity [OR 1.39 (1.15, 1.69)] were more likely to receive SGLT2i, while those with pre-existing PAD [OR 0.75 (0.60, 0.94)] or CKD [OR 0.72 (0.58, 0.88)] were less likely to receive SGLT2i. We did not observe any association between pre-existing HF [OR 1.10 (0.85, 1.40)] or HFrEF [OR 0.86 (0.59, 1.27)] and SGLT2i prescriptions. Compared to blacks, whites [OR 1.64 (1.11, 2.51)] were more likely to receive GLP-1RA therapy, as were obese patients [OR 1.91 (1.50, 2.46)] while patients with cerebrovascular disease [OR 0.59 (0.32, 0.99)] were less likely to receive GLP-1RA (Table 2-4).

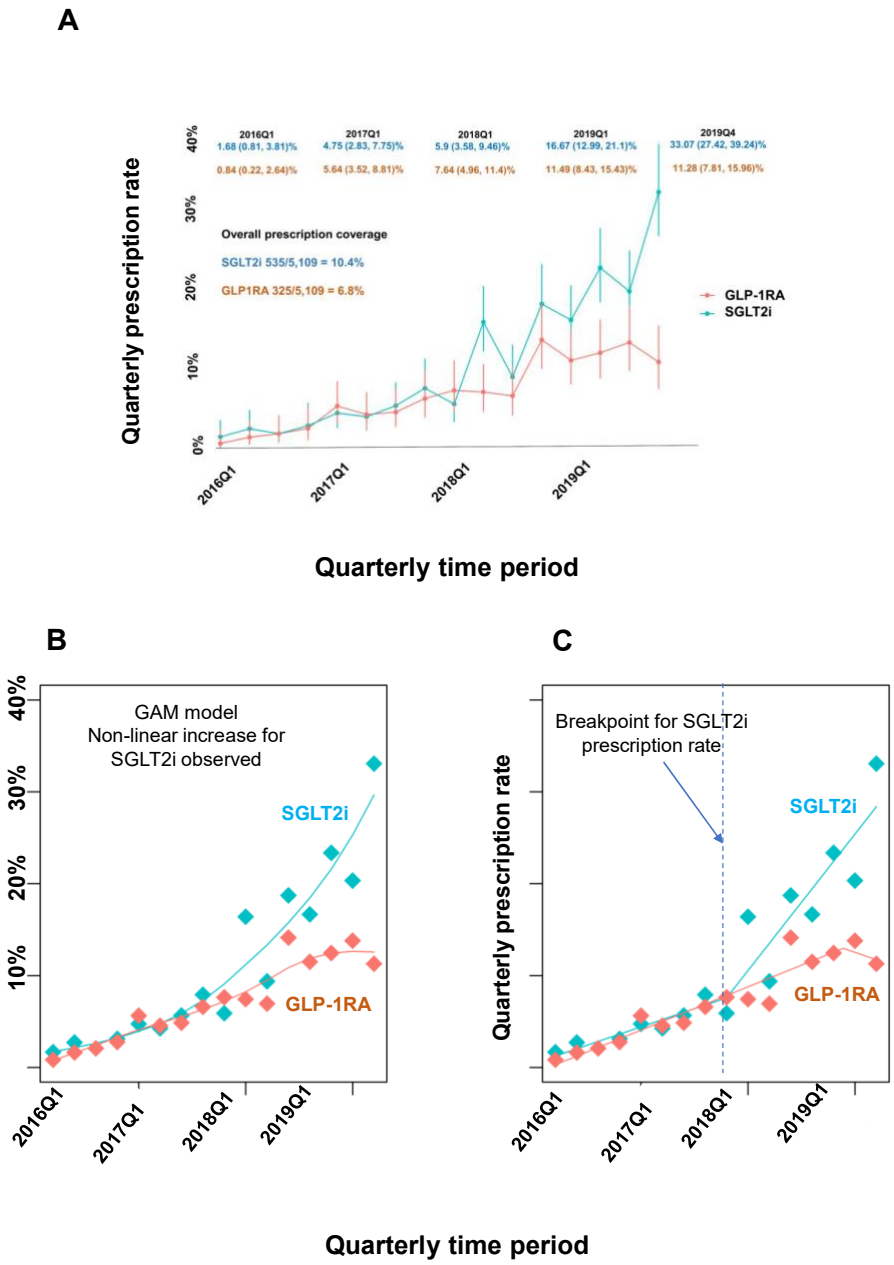


Figure 2-4. Prescription rates for SGLPT2i and GLP-1RA in the study period

The overall prescription coverage for both drugs (SGLT2i – 10.4% and GLP-1RA – 6.8%) was low. the quarterly prescription rates increased for both SGLT2i (1.6% (2016 Q1) to 32% (2019 Q4)) and GLP-1RA (0.8% (2016Q1) to 11.2% (2019Q4)) during the 4-year study period. (B) We observed a non-linear increase in SGLT2i prescriptions rates (GAM model smoothing parameter p-value = 0.03), which was clear from 2018Q1. (C) Exploratory breakpoint analysis demonstrates a breakpoint of 2018Q1 for SGLT2i prescription rates; while GLP-1RA prescription rates also increased, the model did not define a breakpoint for this data.

From 2016 Q1 to 2019 Q4, prescription rates increased for both medications, however, this effect was far greater for SGLT2i (20-fold increase, from 1.6% to

33%) than GLP-1RA (14-fold increase, from 0.8% to 11.2%). Since 2018 Q1, we observed a non-linear increase in prescription rates for SGLT2i (GAM smoothing parameter p-value: 0.03). While GLP-1RA prescriptions also increased over time, they did not increase with the same rate and prescription rates appear to stabilize from 2019 Q1. The exploratory breakpoint analysis model further supports the GAM model by defining 2018 Q1 as the breakpoint for SGLT2i prescriptions (Figure 2-4).

CONCLUSIONS

From over 5000 patients receiving CABG at 40 different VA medical centers, we observed low utilization of SGLT2i or GLP-1RA therapy after surgery. SGLT2i was more likely to be prescribed vs GLP-1RA and prescription rates for SGLT2i rapidly increased since 2018 Q1.

Current guidelines recommend SGLT2i or GLP-1RA for all patients with T2DM and established ASCVD (Cosentino et al., 2020, Das et al., 2018). In CABG patients, T2DM is independently associated with future cardiovascular risk (Holzmann et al., 2015), thus, surgery provides an opportunity to initiate guideline-directed care. Therefore, it is unfortunate that the overall prescription rates among CABG patients are not higher than T2DM with stable coronary artery disease (Hofer et al., 2021). While the observed 20-fold increase in SGLT2i use over a four-year study period is encouraging, two thirds of patients with T2DM undergoing CABG remained untreated with either recommended drug, suggesting a significant opportunity to improve cardiovascular outcomes in this high-risk group. Like a prior study from Denmark, we observed higher prescription rates for SGLT2i compared with GLP1-RA(Knudsen et al., 2020). Possible reasons for preferring SGLT2i in our study may be the advantage of oral therapy and more familiarity among cardiologists for SGLT2i. Drug cost is unlikely to play a role, as Veterans have the same co-pay for either medication.

Increased median household income was associated with SGLT2i use, while obesity was associated with GLP-1RA use. Compared to black patients, whites were also more likely to receive GLP-1RA therapy. These findings support prior observations from commercially insured patients (Eberly et al., 2021). That

these socio-economic disparities should exist among Veterans is perhaps surprising, as co-pay amounts are highly subsidized. However, data from Denmark, a country with a universal healthcare system also report similar observations (Falkentoft et al., 2022). SGLT2i use was lower among patients with CKD and PAD, both high risk subgroups, that derive high absolute benefits with SGLT2i therapy (Barraclough et al., 2021, Barraclough et al., 2022). While the low use of SGLT2i use in PAD patients is likely related concerns of increased amputation rates observed in the CANVAS trial, neither the CREEDENCE trial nor results from large retrospective data support these findings (Paul et al., 2021, Perkovic et al., 2019).

Retrospective data analysis, a predominantly male cohort and the reliance on pharmacy fill data are limitations of our study. Our study is, however, likely, the first to evaluate the use of SGLT2i / GLP-1RA among patients with T2DM following CABG, a high-risk cohort, with considerable potential to benefit from receiving either cardio-protective agent.

In conclusion, between 2016 and 2019, SGLT2i use, and to a lesser extent GLP1-RA use, increased substantially among US Veterans undergoing CABG, with SGLT2i use accelerating rapidly since 2018. However, socio-economic disparities exist and opportunities for improvement remain.

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2.3 Appendix

Table 2-1. Covariates included in our regression analysis.

This table presents definitions for some of the variables included in our regression models.

Covariate	Definition used for our study
Type 2 Diabetes Mellitus	The presence of the ICD 10 code (E11x) in at least 1 inpatient or 2 outpatient visits prior to surgery.
Heart failure	Defined as any outpatient visits with the following ICD10 codes as primary/secondary diagnoses codes in the covariate assessment window or as secondary diagnoses codes at the index visit: 'I09.81%' 'I11.0%' 'I13.0%' 'I13.2%' 'I50.1%' 'I50.20%' 'I50.21%' 'I50.22%' 'I50.23%' 'I50.30%' 'I50.31%' 'I50.32%' 'I50.33%' 'I50.40%' 'I50.41%' 'I50.42%' 'I50.43%' 'I50.810%' 'I50.811%' 'I50.812%' 'I50.813%' 'I50.814%' 'I50.82%' 'I50.83%' 'I50.84%' 'I50.89%' 'I50.9%
Heart failure with a reduced ejection fraction (HFrEF)	Patients with a diagnosis of heart failure and a baseline preoperative left ventricular ejection fraction < 45% were classified as HFrEF
Chronic kidney disease	Defined as a baseline preoperative eGFR < 60 ml/min/m2. Each patient's serum creatinine value (most recent value prior to surgery) was available and the CKD-EPI creatinine equation was used to calculate the estimated glomerular filtration rate (eGFR).
Peripheral arterial disease	These covariates are directly available from the VASQIP (VA surgical quality initiative project) database
Cerebrovascular disease	
Pre-operative left ventricular systolic function	The preoperative left ventricular systolic function was obtained from the VASQIP database. The most recent value prior to the surgery is recorded in VASQIP. A surface echocardiogram is routinely performed as part of the pre-operative evaluation for all patients prior to CABG.
Race and ethnicity	These are self-reported at the time of the admission for surgery
Neighborhood deprivation index (NDI)	The neighbourhood deprivation index, measured on a continuous scale from 0 (least deprived) to 1 (most deprived), is derived using the following 6 census-tract measures: fraction of the population below the poverty level, median household income, fraction of the population with at least a high-school education, fraction of the

	population without health insurance, fraction of the population receiving public assistance income, and fraction of vacant houses in that zip code. Each patient's zip code at the time of admission for surgery was obtained and linked to the published CDI1
Zip code derived median household income	The median household income was obtained from the American Community Survey 5-year estimates2

Table 2-2 This table presents the baseline characteristics for our study cohort

*Missing data: LVEF (125, 2.4%), HbA1c (472, 9.2%), Area deprivation index (123, 2.4%), Median household income (123, 2.4%). Abbreviations; HFrEF – heart failure with reduced ejection fraction. LVEF – left ventricular ejection fraction, * median (interquartile range)*

Baseline Characteristics	Counts (percentage)
Age *	68 (63, 71)
Age group	
< 50 years	106 (2)
50 – 60	811 (15.9)
61 – 70	2700 (52.8)
71 – 80	1383 (27.1)
> 80 years	109 (2.2)
Female sex	83 (1.6)
Race	
White	3974 (77.8)
Black	638 (12.5)
Others	497 (9.7)
Hispanic Ethnicity	591 (11.6)
Area Deprivation index *	0.38 (0.31, 0.44)
Median household income (zip code derived) *	$51,036 ($42,225, $63,727)
Body mass index	31 (27.61, 35)
Obese (BMI > 30 kg/in^2)	2936 (57.5)
Chronic kidney disease	1973 (38.6)
Heart failure	1319 (25.8)
HFrEF	463 (9)
Chronic obstructive pulmonary disease	1454 (28.5)
Peripheral arterial disease	1426 (27.9)
Cerebrovascular disease	348 (6.8)
Poly-vascular disease	1648 (32.3)
Atrial fibrillation	1217 (23.8)
Prior myocardial infarction	2840 (48.5)
Multi-vessel coronary artery disease /Left main disease	3306 (64.7)
Preoperative LV systolic function	
LVEF $\geq$ 0.55	2977 (58.2)
0.45 – 0.54	957 (18.7)
0.40 – 0.44	340 (6.6)
0.35 – 0.39	279 (5.4)
$\leq$ 0.35	431 (8.4)
Pre-operative HbA1c (%) *	7.5 (6.7, 8.4)
Baseline Anti-diabetes therapy	
Metformin	3189 (62.4)
Insulin	2794 (54.6)
Sulphonylureas	1541 (30.6)
DPP4i	423 (8.2)

Table 2-3. Quarterly prescriptions in the study period for SGLT2i and GLP-1RA

Time - period	Total CABG patients per Quarter	New SGLT2i prescriptions	SGLT2i prescription rates per Quarter	New GLP-1RA prescriptions	GLP-1RA prescription rates per Quarter
2016Q1	357	6	1.68 (0.81, 3.81)	3	0.84 (0.22, 2.64)
2016Q2	367	10	2.72 (1.39, 5.11)	6	1.63 (0.67, 3.7)
2016Q3	336	7	2.08 (0.92, 4.43)	7	2.08 (0.92, 4.43)
2016Q4	289	9	3.11 (1.53, 6.03)	8	2.77 (1.29, 5.59)
2017Q1	337	16	4.75 (2.83, 7.75)	19	5.64 (3.52, 8.81)
2017Q2	352	15	4.26 (2.49, 7.08)	16	4.55 (2.71, 7.43)
2017Q3	370	21	5.68 (3.63, 8.68)	18	4.86 (2.99, 7.72)
2017Q4	303	24	7.92 (5.25, 11.71)	20	6.6 (4.18, 10.17)
2018Q1	288	17	5.9 (3.58, 9.46)	22	7.64 (4.96, 11.4)
2018.Q2	323	53	16.41 (12.63, 21.01)	24	7.43 (4.92, 11)
2018Q3	288	27	9.38 (6.38, 13.49)	20	6.94 (4.4, 10.69)
2018Q4	283	53	18.73 (14.45, 23.87)	40	14.13 (10.4, 18.87)
2019Q1	348	58	16.67 (12.99, 21.1)	40	11.49 (8.43, 15.43)
2019Q2	321	75	23.36 (18.92, 28.46)	40	12.46 (9.15, 16.7)
2019Q3	290	59	20.34 (15.96, 25.54)	40	13.79 (10.15, 18.43)
2019Q4	257	85	33.07 (27.42, 39.24)	29	11.28 (7.81, 15.96)

Table 2-4. Factors associated with SGLT2i and GLP1-RA prescription

We fit two separate multivariable generalized logistic regression models to study the association between baseline characteristics and the use of SGLT2i or GLP-1RA within 1 year after coronary artery bypass Abbreviations: HFrEF – heart failure with reduced ejection fraction; Both models include a covariate for hospital identifier

	SGLT2i prescription		GLP-1RA prescription	
Covariate	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age (for every 10-year increase) *	0.75 (0.66, 0.85)	< 0.001	0.83 (0.71, 0.97)	0.02
Female Sex **	0.85 (0.39, 1.65)	0.66	1.79 (0.85, 3.39)	0.09
Race (Ref: Black)				
-White	1.09 (0.81, 1.47)	0.55	1.64 (1.11, 2.51)	0.01
-Others	1.13 (0.76, 1.68)	0.52	1.78 (1.06, 3.01)	0.02
Hispanic ethnicity	1.28 (0.94, 1.72)	0.10	0.80 (0.52, 1.18)	0.29
Neighborhood Deprivation index (for every 0.1 increase)	1.19 (0.98, 1.44)	0.07	1.07 (0.84, 1.35)	0.55
Median household income (for every $5,000 increase)	1.08 (1.03, 1.13)	< 0.001	1.03 (0.97, 1.09)	0.29
Chronic Kidney Disease	0.72 (0.58, 0.88)	< 0.001	1.13 (0.90, 1.42)	0.27
Heart Failure	1.10 (0.85, 1.40)	0.42	1.19 (0.88, 1.57)	0.23
HFrEF	0.86 (0.59, 1.27)	0.62	0.71 (0.43, 1.13)	0.68
Peripheral Arterial Disease	0.75 (0.60, 0.94)	0.01	0.93 (0.72, 1.20)	0.61
Cerebrovascular Disease	0.90 (0.60, 1.30)	0.59	0.59 (0.32, 0.99)	0.06
Obesity	1.39 (1.15, 1.69)	< 0.001	1.91 (1.50, 2.46)	< 0.001

2.4 Author Declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	Trends in Prescriptions of Cardioprotective Diabetic Agents After Coronary Artery Bypass Grafting Among U.S. Veterans. Deo SV, McAllister DA, Al-Kindi S, Elgudin Y, Chu D, Pell J, Sattar N. Diabetes Care. 2022 Dec 1;45(12):3054-3057. doi: 10.2337/dc22-0570. PMID: 36256925 SVD, YE – Louis Stokes Cleveland VA Medical Center, Cleveland USA SAK – Houston Methodist Hospital, Houston, USA DAM, NS, JP, SVD – University of Glasgow, Glasgow UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	**SVD, JP,NS, DAM**
Data Curation	SD
Formal Analysis	SD
Investigation	SD
Methodology	SD,JP,NS, DAM,SAK
Project Administration	JP,NS
Visualisation	SD
Writing - original draft	SD,SAK
Writing - review & editing	JP,NS,SAK,YE,DC

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 3: Paper 2

3 Disparities in PCSK9 inhibitor initiation among US Veterans with peripheral arterial disease or cerebrovascular disease.

3.1 Preface

In the prior chapter, I investigated and reported that the use of SGLT2i and GLP1-RA post-CABG in US Veterans was low. Both these drugs are considered as first-line therapy for patients with type 2 diabetes. In this chapter, I will evaluate patient-, institution-, and community-level factors that may contribute towards this suboptimal use. Therefore, as a use-case scenario, the study presented here analysed PCSK9i initiation in a large cohort of US Veterans with stable ASCVD. As already stated, in Chapter 1, LLT to achieve the recommended LDL-C concentration remains among the most important arms for secondary prevention in ASCVD patients. While statins are the first-line LLT for ASCVD patients, PCSK9i is recommended for those patients that cannot tolerate statin therapy or need add-on therapy to achieve their LDL-C target. In the FOURIER trial, Evolocumab reported a 59% reduction in the median baseline LDL-C levels (Sabatine et al., 2017). However, PCSK9i are expensive and in the US healthcare system, the high denial rates of patient claims by private insurance providers have hindered their wider use (Myers et al., 2019) (MacDougall et al., 2024). However, PCSK9i therapy is available for $33 / month via the VA pharmacy, which is a fraction of the cost that patients with private insurance need to pay. Therefore, I hypothesized that the use rate for PCSK9i among eligible US Veterans would be higher than that observed among other cohorts in the US. Hence, in this study, I analysed the initiation rate for PCSK9i therapy in US Veterans with stable ASCVD nationwide and reported factors that were associated with non-initiation of PCSK9i.

3.2 Published Manuscript

Citation

Disparities in PCSK9 Initiation Among US Veterans with Peripheral Arterial Disease or Cerebrovascular Disease. Deo SV, McAllister D, LaForest S, Altarabsheh S, Elgudin YE, Dunlay S, Singh S, Parikh S, Sattar N, Pell JP. Am J Cardiovasc Drugs. 2023 May;23(3):311-321. doi: 10.1007/s40256-023-00576-7. Epub 2023 Mar 22. PMID: 36947397

Manuscript

ABSTRACT

Aims: Effective lipid lowering is essential in peripheral arterial (PAD) and cerebrovascular (CeVD) disease patients. Proprotein convertase subtilsin/kexin type 9 inhibitors (PCSK9i) efficiently lower low-density lipoprotein (LDL) levels; however, use in PAD and CeVD patients is limited. Therefore, our aim was to evaluate the use of PCSK9i among US Veterans and compare rates between patients with PAD, CeVD, and coronary artery disease (CAD).

Methods and Results: We evaluated PCSK9i initiation (2016 – 2019) in US Veterans with CAD, PAD or CeVD treated at 124 VA hospitals. We fit a hierarchical logistic regression model to evaluate the association of the patient's primary diagnosis, baseline low density lipoprotein cholesterol levels (LDL-C), socioeconomic indicators, and the Department of Veteran Affairs (VA) medical centre enrolment with PCSK9i initiation.

Of 519,566 patients with atherosclerotic vascular disease, 337,766 (65%), 79,926 (15%) and 101,874 (20%) had CAD, PAD and CeVD. Among 2,115/519,566 (0.4%) initiated on PCSK9i therapy, 84.3% had CAD, while only 7.2% and 8.5% had PAD and CeVD respectively. Compared to CAD patients, PAD [OR 0.50 (0.36 – 0.70)] and CeVD [OR 0.24 (0.15 – 0.37)] were less likely to receive PCSK9i. Relative to under $40K per year, PCSK9i initiation was higher if earning $40,000 - $80,000 [OR 1.13 (1.01 – 1.27)] or > $80,000 [OR 1.41 (1.14 – 1.75)]. Even moderate

community deprivation [OR 0.87 (0.77 – 0.97)] was associated with lower PCSK9i therapy.

Conclusions: Adjusted for LDL-C levels, PAD and CeVD patients are much less likely to receive PCSK9i therapy. Despite low co-pay, PCSK9i initiation rates among US veterans, nationwide, is low, with household income and community deprivation appearing to predict PCSK9i use.

1.INTRODUCTION

Effective lipid lowering therapy (LLT) is an important component of guideline-directed medical therapy for patients with atherosclerotic vascular disease (ASCVD). The American Heart Association/American College of Cardiology (AHA/ACC) 2018 guideline recommends the use of high intensity statin therapy in all patients < 75 years with ASCVD. Furthermore, in patients deemed 'very high risk' for recurrent vascular events, AHA/ACC recommend a target LDL-C concentration < 70 mg/dl which, when required, may be achieved by the addition of non-statin drugs to maximally tolerated statin therapy (Grundy et al., 2019). Current guidelines support adding ezetimibe first, followed by proprotein convertase subtilsin/kexin type 9 inhibitors (PCSK9i) (Grundy et al., 2019). Both drugs, ezetimibe(Baigent et al., 2011, Cannon et al., 2015, Sakuma et al., 2019) and PCSK9i (Sabatine et al., 2017, Schwartz et al., 2018), have demonstrated a favourable risk reduction in cardiovascular event rates for patients with established ASCVD. However, a recent study, using insurance claims data from 18 health systems, reported that, of all eligible patients, only 3% and < 1% were treated with ezetimibe and PSCK9i respectively (Chamberlain et al., 2019). Similarly low rates were reported in the US National Practice Innovation and Clinical Excellence (PINNACLE) registry (Blumenthal et al., 2021). Insurance coverage and drug cost continue to remain important barriers to the wider use of PCSK9i in the US (Hess et al., 2017). However, it is unclear whether PCSK9i initiation rates are any higher in a low co-pay healthcare system like the Department of Veteran Affairs (VA). Also, data comparing the PCSK9i use rate in

coronary artery disease (CAD), peripheral arterial disease (PAD) or cerebrovascular disease (CeVD) sub-groups is limited.

The Veterans Health Administration (VA), with more than 1,200 health care facilities, is the largest single-payer healthcare system in the United States (Administration, September 28, 2021). With close to 9 million annual enrolees and an ageing multi-morbid patient cohort, VA medical centres treat many patients with established ASCVD. Furthermore, veterans receive expensive proprietary medications at very low co-pay rates from the VA pharmacy benefits program (Administration, 2021b). Alirocumab, the preferred PCSK9i drug approved for treatment at VHA medical centres, is provided to patients with a maximum $33 monthly co-pay (Administration, 2021b). An earlier cohort study using 2018-2019 data from US Veterans provided an overview regarding PCSK9i use in VA centre, reporting factors associated with the non-initiation of PCSK9i and variation in regional treatment patterns. This analysis builds on prior data by evaluating centre-level variation, temporal changes in PCSK9i use, and more specifically evaluate the use of PCSK9i use in patients with pre-existing PAD, CeVD or poly-vascular disease (Derington et al., 2021). We performed a nationwide longitudinal cohort study of US veterans receiving outpatient care for PAD, CAD or CeVD with the aim to evaluate the following: (1) What clinical and socio-economic patient-level factors were associated with the initiation of PSCK9i? and (2) Were there any differences in PCSK9i initiation between the three disease sub-groups studied (CAD, PAD and CeVD)?

2. METHODS

2.1 Data Source and Study Design: This retrospective, cohort study with individual patient linkage was performed using electronic health records, pharmacy, laboratory, and vital status information stored in VINCI (VA National Computing infrastructure). The study was approved by the Louis Stokes Cleveland VA medical centre institutional review board (CY20-030) and individual patient consent was waived. PCSK9i agents were approved for therapy by the FDA in September 2015. Therefore, the cohort enrolment window for our study was chosen as between 1st January 2016 and 31st December 2019, with the

first outpatient visit date with the primary diagnosis of PAD, CAD, or CeVD during this period defined as their index date. The covariate

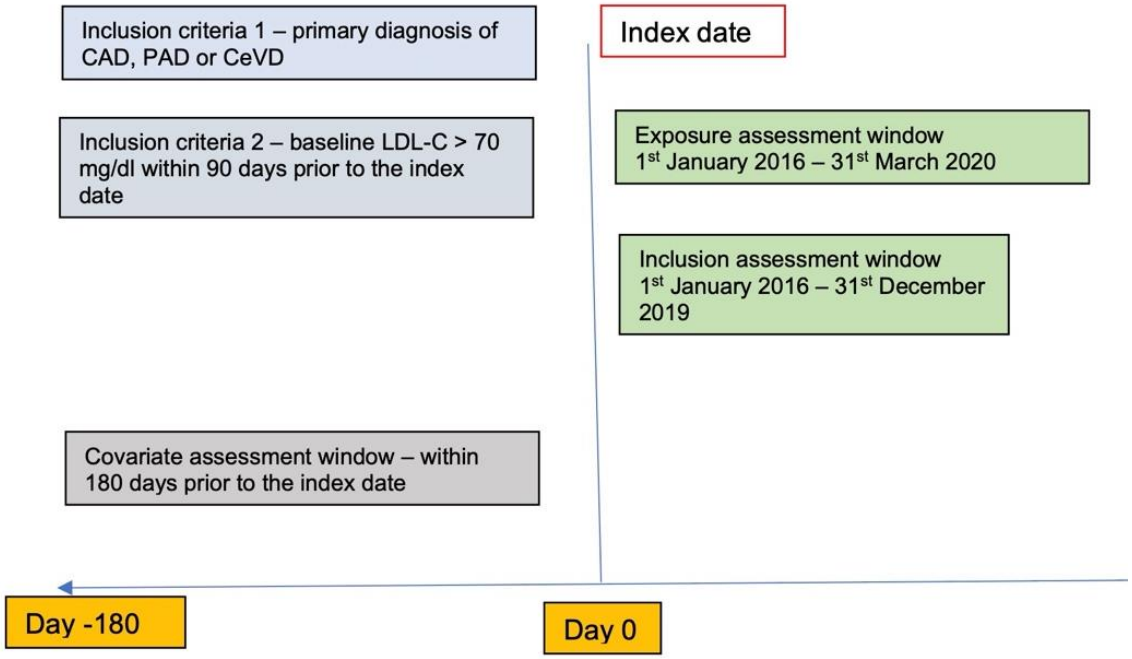

Figure 3-1. This figure presents the covariate and exposure assessment window for our study

assessment window was defined as within 180 days prior to the patient's index date. The study exposure assessment window was defined as between 1st January 2016 and 31st March 2020 inclusive, therefore, extending 90 days beyond the inclusion assessment window (Figure 3-1). The additional 90-day time-period was chosen a-priori, so that patients could potentially receive escalation of LLT in a stepwise manner. For those that were not on statin therapy on their index date, a 90-day period allowed for the initiation of maximally tolerated statin therapy, measurement of LDL-C and further escalation as needed to target appropriate LDL-C concentrations.

2.2 Cohort Development: Using the international Classification of Disease 10th version codes (ICD-CM), we created the study cohort of patients with the primary diagnosis of CAD, PAD or CeVD receiving outpatient care at VA medical

centres nationally (Figure 3-2) (ICD codes are available at: https://github.com/svd09/PCSK9i-paper). For each patient, the LDL-C concentration within the covariate assessment window that was closest to the index date was defined as their baseline LDL-C concentration. Patients with missing LDL-C concentrations (n = 355,288) or those receiving PCSK9i prior to their index date (n = 224) were excluded. We also limited the study cohort to those with baseline LDL-C concentrations ≥ 70 mg/dl, as these individuals are eligible to receive PCSK9i therapy.

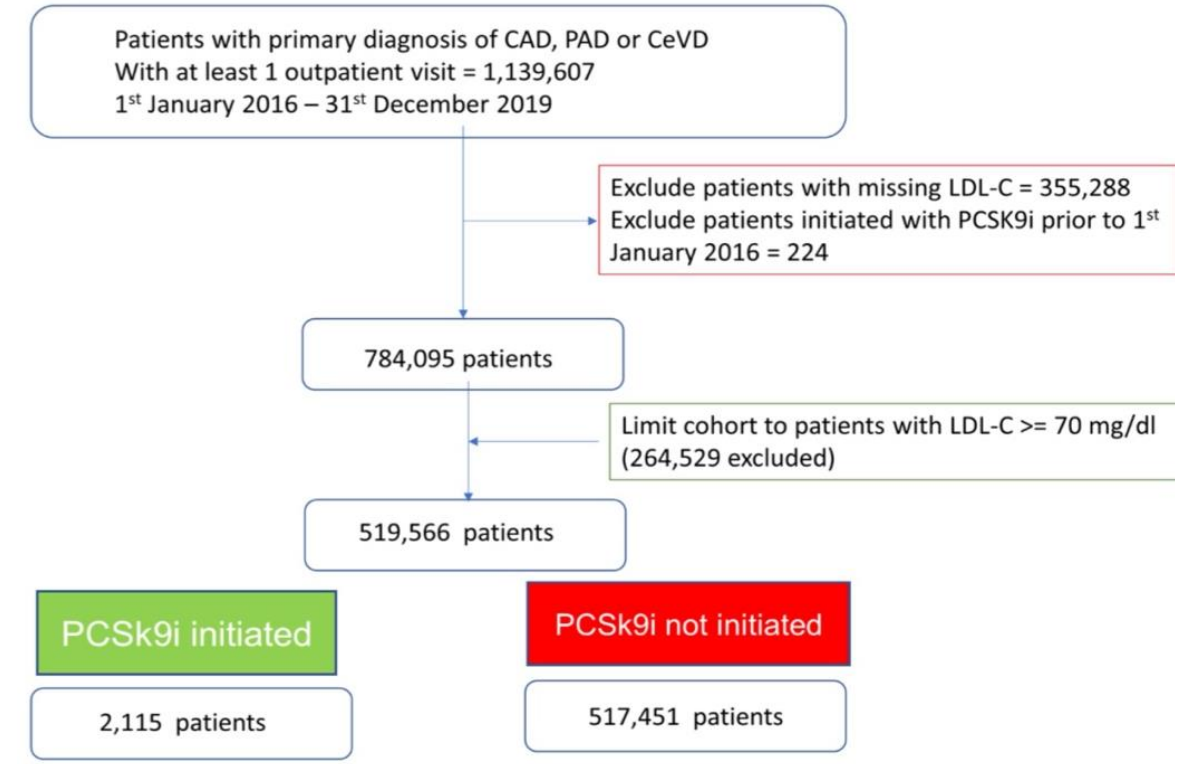

Figure 3-2. Flowchart outlining the steps in the cohort selection

2.3 Identification of Covariates: We used data from inpatient and outpatients' visits within the covariate assessment window to collect information on patient level covariates, namely, age at index visit, sex, self-reported race, presence of diabetes mellitus, hypertension, chronic kidney disease, atrial fibrillation, smoking status and prior history of myocardial infarction or percutaneous intervention (Table S1). Age at index visit into 10-yearly groups as follows: < 60 years, 60 – 70 years, 71 – 80 years, > 80 years. We defined 'poly-vascular disease' as patients with combined CAD/PAD or CAD/CeVD. Using the 2018 AHA/ACC criteria we also identified patients at 'very high risk' for a recurrent adverse vascular event(Grundy et al., 2019) (Table 3-1). We obtained the

residential zip code-derived median household income for each patient from the US Department of Housing and Urban Development (HUD), US Census Bureau; based on eligibility threshold from the Patient Protection and Affordable Care Act, low, middle, and high median household income were defined as < $ 40,000/year, $ 40,000 – $ 80,000/year and > $80,000/year (January 18, 2018.). The community deprivation index (CDI) is a marker of the social determinants of health, which are associated with adverse cardiovascular outcomes(Huded et al., 2021, Mathews et al., 2022). Therefore, we linked patients to their CDI score using their residential zip code. The CDI, measured on a continuous scale, is derived using the following 6 census-tract measures: fraction of the population below the poverty level, median household income, fraction of the population with at least a high-school education, fraction of the population without health insurance, fraction of the population receiving public assistance income, and fraction of vacant houses in that zip code. The eventual CDI is a rescaled value between 0 (least) and 1 (most deprived) (Brokamp et al., 2019). Based on their rescaled CDI scores, patients were then grouped into the following categories: I (least): CDI < 0.33, II (moderate): CDI 0.33 – 0.66, and III (most) deprived: CDI 0.67 – 1.00.

2.4 Identifying baseline LLT: Baseline LLT was identified using pharmacy fill data within 6 months prior to the patients index date. Applying the AHA/ACC statin intensity criteria to the filled statin type and dose data, patients were classified into the following mutually exclusive groups: not receiving statin therapy, receiving low/moderate intensity statin therapy, or receiving high-intensity statin therapy (Grundy et al., 2019). We also identified patients that were receiving ezetimibe therapy at or prior to their study inclusion.

2.5 Endpoint: The endpoint studied was the initiation of PCSK9i during the observation window. Patients that received at least 1 fill for PCSK9i therapy during the observation window comprise the ‘PCSK9i initiated’ group, while the remainder formed the ‘PCSK9i not initiated’ group. The first fill date for PCSK9i was defined as their initiation date.

2.6 Statistical Analyses: Continuous variables demonstrated a skewed distribution, hence were reported as median (interquartile range); categorical

data were presented as counts (percentages). The Wilcoxon rank sum test and the χ^2 test were used to compare continuous and categorical data between groups respectively. Baseline characteristics between CAD, PAD and CeVD groups were evaluated by separately comparing the PAD and CeVD groups with the CAD group. The standardized difference (SD) was used as the measure to evaluate if there was meaningful difference between groups, as it is a better measure than the p-value when dealing with large sample sizes (Austin, 2009). A SD > 0.1 is conventionally considered to imply meaningful difference between groups. We calculated the PCSK9i initiation rate for each VA medical centre overall and for each group (CAD, PAD and CeVD). To assess factors associated with the initiation of PCSK9i, a multivariable hierarchical random intercept regression model was fitted with PCSK9i initiation as the endpoint. The variable identifying the patient's VA medical centre was included as a random effect, while all other covariates were fitted as fixed effects. The patient's primary diagnosis (CAD, PAD or CeVD) was the main dependent variable entered in the model while demographic characteristics (age at index visit, sex, self-reported race), clinical characteristics (DM, hypertension, smoking status, AF, COPD, heart failure, chronic kidney disease, presence of poly-vascular disease, history of myocardial infarction, prior PCI, baseline LDL-C concentration and familial hypercholesterolemia), socioeconomic factors (median annual household income category, community deprivation index category) and baseline drug therapy (LLT, ezetimibe therapy) were forced into the model as confounders. Regression models were fit with STATA 17 (The STATA Corp, Station College, Texas). Marginal (population averaged) results were obtained using the *'margins'* and *'contrast'* commands in STATA. Patients in our cohort underwent outpatient care at 124 different VA outpatient centres. To adjust for the centre-level variation, a hierarchical logistic regression model was fit with PCSK9i initiation as the binomial endpoint. The variable defining hospital ID was fit as random effects and allowed a random intercept. The random effects were assumed as normally distributed. Three models were iteratively fit as part of our explanatory model building process.

Model 1 = hierarchical model (level 1: age fit as a continuous + other covariates(binary/categorical), level 2: VA medical centre as random effect)

Model 2 = hierarchical model (level 1: age stratified into categories (as described below) + all other covariates, level 2: VA medical centre fit as a random effect)

Model 3 (reported model) = hierarchical model (level 1: age fit as a categorical variable + all other covariates + interaction term between primary diagnosis and LDL-C category level 2: VA medical centre fit as random effects).

At each step, likelihood ratio tests were used to compare nested models. We obtained the coefficients and standard error for all covariates included in the mixed effect models and used these to calculate the Odds ratio and 95% confidence interval. Results for the random effect term included in the models were reported as the median odds ratio. Missing data were present in two variables (median household income 3.4% and community deprivation index 1.5%). Missing values for both were imputed at their mode values. All other variables were complete. The AHA/ACC 2018 cholesterol management guidelines for secondary prevention differs in its recommendation for patients $\leq$ and > 75 years (Grundy et al., 2019). Therefore, as a sensitivity analysis, our final model was refit to a subset of our cohort $\leq$ 75 years at their index visit. Statistical analyses were performed using R 4.0.2 (The R Foundation for Statistical Computing, Austria) and STATA 17 (The STATA Corporation, Station College, Tx). Further details regarding statistical methods are provided in the supplementary appendix. The study is designed and reported according to the STROBE guidelines (Vandenbroucke et al., 2009).

2.7 Data availability statement: The study was approved by the Research and Development committee approval # 19-045. Investigators credentialled for research at the Veterans Affairs Department can obtain access to the data as per departmental guidelines. Data cannot be shared for ethical/privacy reasons. Code used for statistical analyses can be obtained from the corresponding author on reasonable request.

3. RESULTS

3.1 Overview of Study Cohort:

Between 2016 and 2019, 519,566 patients [age – median 74 (IQR - 68,80) years, 4% female] with established ASCVD received outpatient care at 124 VHA medical centres. Among them, CAD, PAD and CeVD were the primary diagnoses in 337,766 (65%), 79,926 (15%) and 101,874 (20%) (Table 3-2). DM (46%), chronic kidney disease (14.5%), COPD (20.1%) and poly-vascular disease (26.1%) were most prevalent in the PAD sub-group, while heart failure (9.8%), atrial fibrillation (13.4%) and prior myocardial infarction (3.8%) were most prevalent in CAD patients. The PAD sub-group had the highest percentage of patients (89%) classified as 'very high risk', followed by the CevD (61%) and CAD (59%) sub-groups (Table 3-1). In the overall cohort, the median baseline LDL-C concentration was 97 [IQR: 82,121] mg/dl; 54.7% had an LDL-C between 70 and 100 mg/dl and 18.6% had an LDL-C > 130 mg/dl. While 43.7% were not receiving any statins, 25.1% were on high-intensity therapy. The proportion of patients receiving high intensity statin therapy (CAD 27% vs PAD 21.4% vs CeVD 21.7%) or ezetimibe therapy (CAD 1.2% vs PAD 0.7% vs CeVD 0.7%) was highest in the CAD cohort.

3.2 Observed differences between groups according to PCSK9i use:

During the observation window, 2,115/519,566 (0.4%) were initiated with PCSK9i therapy. Of those, 1,782/2,115 (84.3%) had CAD, while only 152/2,115 (7.2%) and 181/2,115 (8.5%) had PAD and CeVD respectively (Table 3-3). Patients initiated with PCSK9i were likely to be younger (median age: 72 vs 74 years), white (56.7% vs 52.3%) and living in zip codes that had higher median household incomes ($49,257 vs $47,673). While the incidence of diabetes mellitus was similar in both groups (34.8% vs 36.1%), the incidence of heart failure (6.8% vs 8.7%) or CKD (10.4% vs 11.8%) was lower in the PCSK9i initiated group. In the PCSK9i initiated group, 21.5% and 16.8% were on high intensity statins and ezetimibe respectively.

3.3. Centre-level variations in PCSK9i therapy:

During the study period, patients received care at 124 different VA medical centres, with, on average, 4,190 treated at each VA centre. The median PCSK9i initiation rate per centre was 3.27 [IQR:1.52,5.5]/1,000 patients, while the

maximum PCSK9i initiation rate per centre was 17.9/1,000 patients. At 4.26 (IQR: 1.73 – 5.29)/1,000, the CAD sub-group had the highest PCSK9i initiation rate. Both PAD [0.96 (IQR: 0 – 2.58)/1,000] and CeVD [1.11 (IQR: 0 – 2.32)/1,000] sub-groups had substantially lower rates (Figure 3-3). In the CAD sub-group, 78 medical centres had a PCSK9i initiation rate at or above the overall study rate (3.27/1,000 patients). However, this was true for only 22 and 18 centres in the PAD and CeVD sub-groups respectively. We also observed that, independent of patient characteristics, the VHA medical centre also influenced PCSK9i initiation [MOR 1.14 (1.08, 1.21)].

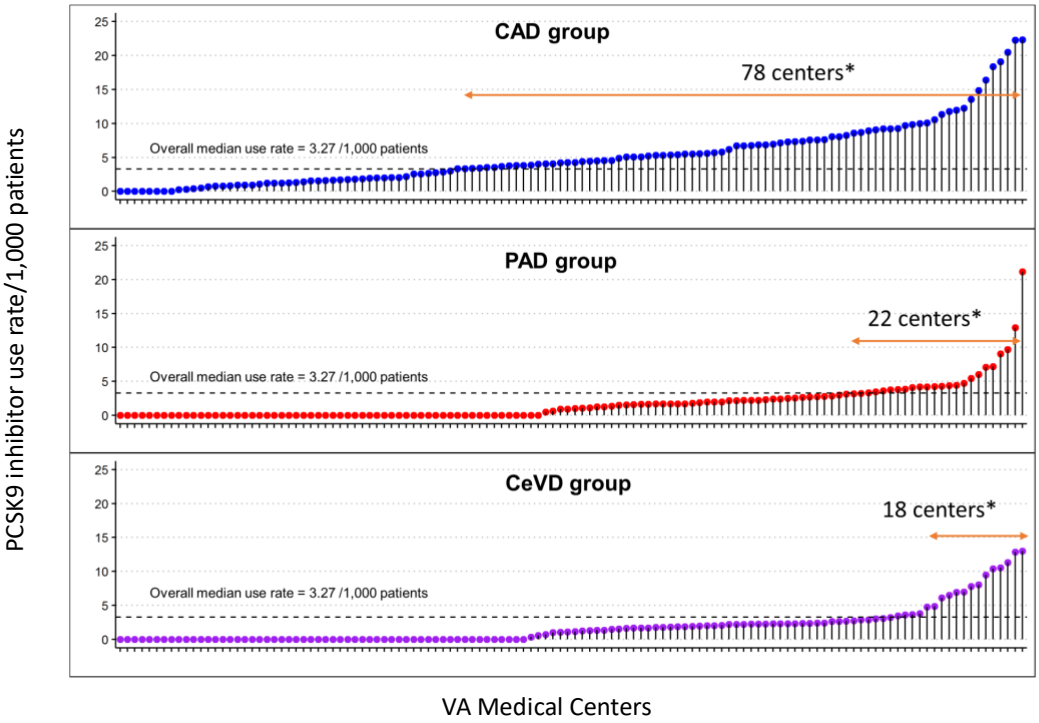

Figure 3-3. The PCSK9i use rate.

The PSCSK9i use rate is plotted for the 124 VA medical centres where patients in our cohort study received treatment. The overall median PCSK9i use rate was 3.27/1,000 patients. The number of VA centres above the median use rate is substantially lower for the PAD and CeVD groups. * Number of VA medical centres at or above the overall median PCSK9i use rate of 3.27/1,000 patients

3.4 Factors influencing PCSK9i initiation:

After adjusting for demographic, clinical, and socioeconomic factors, compared to CAD patients, PAD [OR 0.50 (0.36 – 0.70)] and CeVD [OR 0.24 (0.15 – 0.37)] patients were much less likely to receive PCSK9i therapy. Compared to patients with LDL-C 70 – 100 mg/dl, those with LDL-C 100 – 130 mg/dl [OR 2.92(2.51 – 3.40)] and > 130 mg/dl [OR 10.01 (8.75 – 11.46)] had increased odds of using PCSK9i. However, in each LDL-C category, compared to CAD patients, the odds of PCSK9i initiation were substantially lower in PAD and CeVD patients (Figure 3-4). Even among patients classified as 'very high risk', compared to CAD patients, those with PAD [OR 0.34 (0.28 – 0.41)] or CeVD [OR 0.28 (0.23 – 0.34)] were at much lower odds of receiving PCSK9i initiation. With the age group 60 – 70 years as the reference, younger (< 60 years) [OR 1.16 (1 – 1.35)] and older (71 – 80 years) [OR 1.31 (1.18 – 1.46)] patients had higher odds of receiving PCSK9i therapy (Figure 3-5). Patients with CKD [OR 1.15 (1 – 1.34)] or those classified as 'very high risk' [OR 1.15 (1 – 1.32)] had higher odds of receiving PCSK9i therapy. With the lowest median annual household income tier (< $40,000) as reference, those with an annual household income $40,000 - $80,000 [OR 1.13 (1.01 – 1.27)] and > $80,000 [OR 1.41 (1.14 – 1.75)] were more likely to receive PCSK9i therapy. Compared to those living in the least deprived neighbourhoods, patients that lived in moderately deprived neighbourhoods [OR 0.87 (0.77 – 0.97)] were less likely to receive PCSK9i therapy (Table 3-4). The main results remained the same, even after refitting our model to the subset of patients < 75 years (Table 3-5, Table 3-6).

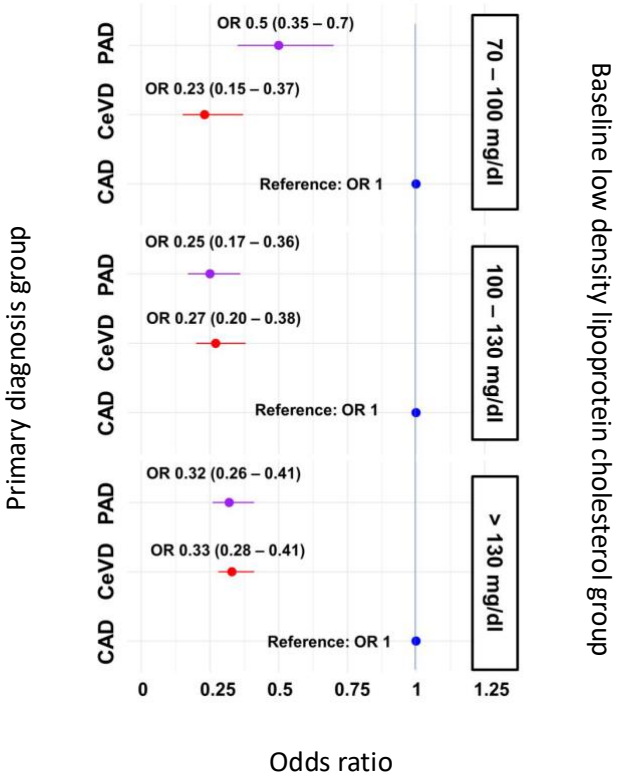

Figure 3-4. PCSK9i use rate according to LDL-C levels

Compared to CAD patients, for each LDL-C category, PAD and CeVD patients were at much less likely to receive PCSK9i therapy. Abbreviations: CAD – coronary artery disease, PAD – peripheral arterial disease, CeVD – cerebrovascular disease. *Odds ratios (with 95% confidence intervals) are provided for each group in brackets with CAD cohort as the reference

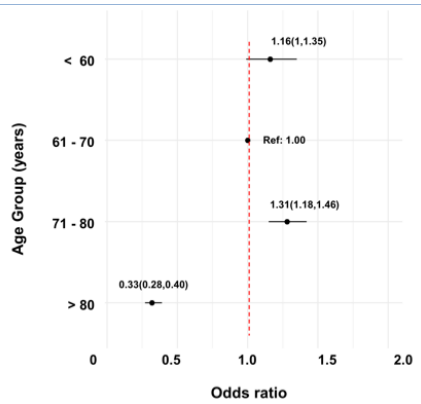

Figure 3-5. Age group and PCSK9i use

Compared to patients aged between 60 and 70 years, both younger (< 60 years) and older patients (71 – 80 years) were at higher odds of receiving PCSK9i therapy.

4. DISCUSSION

We queried data from more than 500,000 patients with ASCVD treated at 124 VA medical centres. In a national cost subsidized healthcare system, we observed a very low initiation rate (3.27 / 1,000 patients) for PCSK9 inhibitors with substantial centre-level variation in PCSK9i initiation. PCSK9i initiation was also inequitable, with lower rates observed in blacks and those with a lower median household income or residing in deprived neighbourhoods. Compared to CAD patients, PCSK9i initiation was also substantially lower in PAD and CeVD patients.

All patients with established ASCVD, irrespective of primary pathology (CAD, PAD or CeVD) are at increased risk of suffering from acute vascular events. Therefore, appropriate lipid lowering therapy is important in PAD and CeVD patients too.(Gerhard-Herman et al., 2017) (Kernan et al., 2014). In the Fourier trial (Sabatine et al., 2017), which first established the clinical benefit of PCSK9i therapy, 14% and 19% of enrolled patients had PAD and CeVD respectively. PCSK9i treated PAD patients had a 21% relative risk reduction in the primary endpoint while those with prior stroke experienced a 21% relative risk reduction in recurrent stroke(Bonaca et al., 2018) (Giugliano et al., 2020). However, despite this established benefit, we observed lower PCSK9i initiation rates in eligible CeVD patients and the lowest in those with PAD. Even in patients with very high LDL-C concentrations (> 130 mg/dl) or those classified as ‘very high risk’, PAD and CeVD patients were much less likely to receive PCSK9i therapy. We also observed that, compared to CAD patients, high intensity statin and ezetimibe therapy rates were substantially lower in the PAD and CeVD patients. These findings, in combination, highlight the suboptimal lipid lowering therapy provided to the PAD and CeVD sub-groups. Like our results, a private insurance claims data, also reported that only 0.1% patients with PAD were receiving PCSK9i therapy (Hess et al., 2021). While the older median age of PAD patients may make less likely to receive PCSK9i, they also have a high incidence of poly-vascular disease, which should, in theory, make them more likely to receive this drug. Also, the appropriate use criteria for PCSK9i in VA centres, introduced in late 2015 after the FDA approval, allow any physician, with justification, to initiate alirocumab therapy (Derington et al., 2021). Therefore, the observed

disease-based disparity in PCSK9i initiation when cost is not a limiting factor is concerning. In 2018, AHA/ACC updated their guideline to recommend a target LDL-C < 70 mg/dl in patients deemed ‘very high risk’ for recurrent vascular events. Using these 2018 AHA/ACC criteria, we observed that, compared to 59% CAD patients, 90% PAD and 61% CeVD patients were ‘very high risk’. Therefore, as per these revised guidelines, a large proportion of PAD and CeVD patients are presently sub-optimally treated.

We observed a negative association between median household income and PCSK9i initiation. This observation, is, partly understandable in patient populations managed through private healthcare, where annual co-pay amounts for PCSK9i may exceed $ 2,000/year (Blumenthal et al., 2021) (Nasir et al., 2019). However, prior research has shown that, compared to zero co-pay, even co-pay amounts as low as $120/year are associated with reduced medication adherence (Ye et al., 2007). A novel value based zero co-pay initiative for patients with chronic disorders has reported lower overall health-care costs (Yuan et al., 2020), Therefore the VA and other health care systems may want to consider extending zero co-pay to patients at the highest clinical risk as these patients may have the highest absolute risk reduction with these costly therapies. Physician outreach, patient empowerment and shared decision making are some tools that may help improve these disparities (Seferovic et al., 2021).

While we observed a very low centre level prescription rate (3.27/1,000 patients), what we report is around a third lower than that (median PCSK9i use rate: 5/1,000 patients) seen in the nationwide US PINNACLE registry, a prospectively collected data warehouse under the stewardship of the American College of Cardiology and Veradigm (Blumenthal et al., 2021). Our findings are also like theirs in many other aspects (Blumenthal et al., 2021). We too found that patients at ‘very high risk’, those having poly-vascular disease or in the higher LDL-C categories had higher odds of receiving PCSK9i therapy. Compared to white patients, black and other ethnic minority patients had lower odds of receiving PCSK9i therapy. Others have also reported lower prescription rates for chronic diseases among black and ethnic minority patients (Briesacher et al., 2003). Also, importantly, like us, they too observed wide variation in PCSK9i

initiation rates between centres (Blumenthal et al., 2021). Our results also show that, for some patients, recommended guidelines regarding stepwise escalation in LLT were not followed. Among PCSK9i initiated patients, only 42% were on statin therapy, with only 20% on high intensity statins. Even after assuming a hypothetical situation wherein 20% of our cohort is statin intolerant, many more patients should be receiving statins prior to PCSK9i initiation (Stroes et al., 2015). Unfortunately, the use of ezetimibe therapy in our cohort was lower than that reported by others (Hines et al., 2018) (Blumenthal et al., 2021). Statin-ezetimibe combination therapies have proven benefit in lowering LDL-C concentrations within 3 months at a fraction of the cost of PCSK9i therapy (Lee et al., 2021). Therefore, this presents another area for future improvement.

Our study had several strengths. We used a large national cohort of more than 500,000 patients, and present results regarding PCSK9i dispensing stratified by the primary type of ASCVD. However, we also recognize specific limitations in our study. Our study evaluated the use of PCSK9i therapy among US veterans. Hence, although national in scope, results may not be generalizable to the private insurance-based healthcare prevalent in the rest of the US. The small percentage of women and an older cohort, are again, inherent limitations of the veteran population. However, our results may still be representative of the wider ASCVD population, as many of our findings mirror those observed in other study populations.

CONCLUSIONS

Our cohort study reported that PCSK9i initiation rates among eligible US veterans receiving care in VA hospitals were very low. Compared to patients with CAD, even after adjusting for baseline LDL-C concentrations, those with PAD or CeVD were, on average, 50% and 74% less likely to receive PCSK9i therapy. Lastly, despite low co-pay rates, household income still influenced the use of PCSK9i among veterans.

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those of the authors. They do not represent the position or policy of the Department of Veteran Affairs or the United States Government.

3.3 Appendix

Table 3-1. This table presents the 2018 AHA/ACC criteria to define patients at 'very high risk' for recurrent ASCVD events

Criteria used by the 2018 AHA/ACC definition for 'very high risk'	Study cohort (N = 519,566)	CAD group (N = 337,766)	PAD group (N = 79,926)	CeVD group (N = 101,874)
Major criteria				
Acute coronary syndrome in the past year	13,136 (2.5)	11,417 (3.4)	756 (0.9)	963 (0.9)
History of myocardial infarction (apart from above)	14,641 (2.8)	12759 (3.8)	827 (1)	1055 (1)
History of ischemic stroke	26,362 (5)	6983 (2.1)	2151 (2.7)	17,228 (16.9)
Symptomatic peripheral arterial disease	109,040 (20.9)	20845 (6.2)	79926 (100)	8269 (8.1)
Minor Criteria				
Age >_65 years	438,903 (84)	285801 (84.6)	67661 (84.7)	85441 (83.9)
Heterozygous familial hypercholesterolemia	2110 (0.4)	1379 (0.4)	340 (0.4)	391 (0.4)
History of prior CABG or PCI	12,405 (2.3)	11398 (3.4)	502 (0.6)	505 (0.5)
Diabetes Mellitus	187,532 (36.1)	109069 (32.3)	46730 (46)	41733 (41)
Hypertension	351,799 (67.7)	230921 (68.4)	52823 (66.1)	68055 (66.8)
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m2)	61,089 (11.8)	36422 (10.8)	11575 (14.5)	13092 (12.9)
Current smoking	78,356 (15)	50859 (15.1)	12063 (15.1)	15434 (15.2)
Persistently elevated LDL-C (LDL-C >100 mg/dL)	235,450 (45.3)	148901 (44.1)	36773 (46)	49776 (48.9)
Heart failure	45,163 (8.7)	33065 (9.8)	5918 (7.4)	6180 (6.1)
Incidence of at least 2 major criteria	74,246 (14.2)	47514 (14.1)	18437 (23.1)	8295 (8.1)
Incidence of at least 2 minor factors	326,176 (62.7)	194827 (57.7)	69794 (87.3)	61555 (60.4)
Incidence of 'Very high risk" category	335,400 (64.5)	201039 (59.5)	71398 (89.3)	62963 (61.8)

Table 3-2. Descriptive information for the whole cohort

Description of the baseline characteristics of our study cohort as well as separately for the CAD, PAD and CeVD groups. Abbreviations: CAD – coronary artery disease, CeVD – cerebrovascular disease, LDL-C – low density lipoprotein type C, MI – myocardial infarction, PAD – peripheral vascular disease, PCI – percutaneous intervention. [a]Standardized differences between groups (SD) > 0.1 is considered significantly different

	Whole Cohort (n = 519,566)	CAD Group (n = 337,766)	PAD Group (n = 79,926)	Standardized Difference* (PAD vs CAD)	CeVD Group (n = 101,874)	Standardized Difference[a] (CeVD vs CAD)
Age (Median [IQR]) years	74 [68, 80]	74 [69, 80]	73 [68, 79]	0.03	74 [68, 80]	0.01
Age group				0.04		0.01
< 60 years	45,383 (8.7)	30,153 (8.9)	6,190 (7.7)		9,040 (8.9)	
60 – 70 years	124,329 (24)	77,208 (22.9)	21,646 (27.1)		25,475 (25)	
71 – 80 years	226,694 (43.6)	149, 615 (44.3)	34,586 (43.3)		42,493 (41.7)	
> 80 years	123, 160 (23.7)	80,790 (23.9)	17,504 (21.9)		24,866 (24.4)	
Males	498,489 (95.9)	326,066 (96.5)	76,357 (95.5)	0.051	96,066 (94.3)	0.107
Self-reported race				0.201		0.206
White	271,938 (52.4)	184,353 (54.5)	38,773 (48.5)		48,812 (47.9)	
Black	45,975 (8.8)	23,191 (6.9)	10,006 (12.5)		12,778 (12.5)	
Others	201,653 (38.8)	130,222 (38.6)	31,147 (39)		40,284 (39.5)	
Diabetes mellitus	187,532 (36.1)	109,069 (32.3)	36,730 (46)	0.283	41,733 (41)	0.181
Systemic hypertension	351,799 (67.7)	230,921 (68.4)	52,823 (66.1)	0.049	68,055 (66.8)	0.033
Heart failure	45,163 (8.7)	33,065 (9.8)	5,918 (7.4)	0.085	6180 (6.1)	0.138
Chronic kidney disease	61,089 (11.8)	36,422 (10.8)	11,575 (14.5)	0.112	13,092 (12.9)	0.064
Atrial fibrillation	67,158 (12.9)	45,097 (13.4)	9,236 (11.6)	0.054	12,825 (12.6)	0.023
Prior MI	14,641 (2.8)	12,759 (3.8)	827 (1)	0.18	1,055 (1.0)	0.18
Prior PCI	12,405 (2.4)	11,398 (3.4)	502 (0.6)	0.197	505 (0.5)	0.21
COPD	91,072 (17.5)	58,489 (17.3)	16,082 (20.1)	0.072	16,501 (16.2)	0.03

Poly-vascular disease	82,471 (15.9)	35,652 (10.6)	20,868 (26.1)	0.41	25,951 (25.5)	0.396
'Very high risk'	335,400 (64.6)	201,039 (59.5)	71,398 (89.3)	0.727	62963 (61.8)	0.047
Median household income group				0.07		0.053
< $40,000	137,133 (27.3)	86,371 (26.4)	22,574 (29.5)		28,188 (28.7)	
$40,000 - $80,000	327,543 (65.3)	215,870 (66)	48,679 (63.6)		62,994 (64.2)	
> $80,000	37,176 (7.4)	24,917 (7.6)	5,309 (6.9)		6,950 (7.1)	
US Region				0.057		0.075
Midwest	108,559 (21.3)	70,596 (21.2)	17,449 (22.4)		20,514 (20.5)	
Northeast	88,443 (17.3)	58,415 (17.6)	14,836 (19.1)		15,192 (15.2)	
South	218,680 (42.8)	142,461 (42.8)	32,235 (41.4)		43,984 (44)	
West	94,892 (18.6)	61,303 (18.4)	13,355 (17.1)		20,234 (20.2)	
Rural location	305,762 (60.1)	206,474 (62.4)	43,114 (55.1)	0.15	56174 (56.3)	0.125
Baseline LDL-C levels (Median [IQR])	97 [82, 121]	96 [81.3, 120]	97.6 [82.6, 120]	0.016	99.6 [83.2, 123]	0.082
Baseline LDL-C category (mg/dl)				0.05		0.096
70 - 100	284,116 (54.7)	188,865 (55.9)	43,153 (54)		52,098 (51.1)	
100 – 130	140,298 (27)	88,132 (26.1)	22,614 (28.3)		29,552 (29)	
> 130	95,152 (18.3)	60,769 (18)	14,159 (17.7)		20,224 (19.9)	
On statin therapy (pre-index window [-180,0] days)	293,682 (56.5)	192,359 (57)	44,856 (56.1)	0.017	56,467 (55.4)	0.031
Statin therapy Intensity				0.142		0.129
No statins	225,884 (43.5)	145,407 (43)	35,070 (43.9)		45,407 (44.6)	
Low/moderate	163,390 (31.4)	101,254 (30)	27,758 (34.7)		34,378 (33.7)	
High	130,292 (25.1)	91,105 (27)	17,098 (21.4)		22,089 (21.7)	
On ezetimibe therapy (pre-index window [-180,0] days)	5,169 (1)	3,921 (1.2)	561 (0.7)	0.048	687 (0.7)	0.051
Year of index visit				0.072		0.108
2016	244,339 (47)	163,806 (48.5)	36,333 (45.5)		44,200 (43.4)	

2017	115,092 (22.2)	74239 (22)	17,515 (21.9)		23,338 (22.9)	
2018	85,825 (16.5)	53772 (15.9)	13,812 (17.3)		18,241 (17.9)	
2019	74,310 (14.3)	45949 (13.6)	12,266 (15.3)		16,095 (15.8)	
Community deprivation index (Median [IQR])	0.38 [0.32, 0.44]	0.38 [0.32, 0.44]	0.38 [0.32, 0.45]	0.1	0.39 [0.33, 0.45]	0.096
Community deprivation index Tertile				0.055		0.056
I (Least deprived)		97,741 (29.3)	21,315 (27.4)		26,878 (26.9)	
II (Moderately deprived)		234,373 (70.3)	56,057 (71.9)		72, 506 (72.5)	
III (Most deprived)		1,496 (0.4)	562 (0.7)		570 (0.6)	

Table 3-3. This table presents the characteristics of patients that were and were not initiated with PCSK9i

	PSCK9i initiated (n = 2,115)	PCSK9i not initiated (n = 517,451)	p-value
Primary diagnosis			< 0.001
CAD	1,782 (84.3)	335,984 (64.9)	
PAD	152 (7.1)	79,774 (15.4)	
CeVD	181 (8.6)	101,693 (19.7)	
Age (Median [IQR]) years	72 [66, 75]	74 [68, 80]	< 0.001
Males	2009 (95)	496,480 (95.9)	0.03
Self-reported Race			< 0.001
White	1,200 (56.7)	270,738 (52.3)	
Black	120 (5.7)	45,855 (8.9)	
Others	795 (37.6)	200,858 (38.8)	
'Very high risk'	1,545 (73.0)	333,855 (64.5)	< 0.001
Heart failure	143 (6.8)	45,020 (8.7)	0.002
Chronic kidney disease	220 (10.4)	60,869 (11.8)	0.057
Diabetes mellitus	735 (34.8)	186,797 (36.1)	0.2
Atrial fibrillation	226 (10.7)	66,932 (12.9)	0.002
Hypertension	1424 (67.3)	350375 (67.7)	0.72
COPD	262 (12.4)	90,810 (17.5)	< 0.001
Prior MI	58 (2.7)	14583 (2.8)	0.88
Prior PCI	103 (4.9)	12,302 (2.4)	< 0.001
Poly-vascular disease	332 (15.7)	82,139 (15.9)	0.84
Baseline LDL-C (Median [IQR]) mg/dl	140 [110, 172.9]	97 [82, 120.2]	< 0.001
Baseline LDL-C category			< 0.001
70-100	374 (17.7)	283,742 (54.8)	
100 - 130	517 (24.4)	139,781 (27.0)	
>130	1,224 (57.9)	93,928 (18.2)	
On statin therapy (pre-index window [-180,0] days)	893 (42.2)	292789 (56.6)	< 0.001
Statin therapy intensity			
No statins	1,222 (57.8)	224,662 (43.4)	
Low/moderate	439 (20.8)	162,951 (31.5)	
High	454 (21.5)	129,838 (25.1)	
On ezetimibe therapy (pre-index window [-180,0] days)	356 (16.8)	4,813 (0.9)	< 0.001
Median household income group			< 0.001
< $40000	507 (24.6)	136,626 (27.3)	

$40,000 - $80,000	1,361 (66)	326,182 (65.3)	
> $80,000	193 (9.4)	36,983 (7.4)	
40000-80000	1361 (66.0)	326182 (65.3)	
US Region (%)			
Midwest	465 (22.2)	108,094 (21.3)	
Northeast	328 (15.6)	88,115 (17.3)	
South	997 (47.5)	217,683 (42.8)	
West	308 (14.7)	94,584 (18.6)	
Community deprivation index (Median [IQR])	0.37 [0.31, 0.43]	0.38 [0.32, 0.44]	< 0.001
Community deprivation index tertile			< 0.001
I (Least deprived)	690 (32.9)	145,244 (28.5)	
II (Moderately deprived)	1,406 (67)	361,531 (71)	
III (Most deprived)	3 (0.1)	2,625 (0.5)	

Table 3-4. Results of the model fit to evaluate PCSK9i initiation

We fit a hierarchical regression model to evaluate factors associated with PCSK9i initiation. After adjusting for center level variation, this table presents the odds ratios for covariates included in the model. Abbreviations: CAD – coronary artery disease, CeVD – cerebrovascular disease, COPD – chronic obstructive pulmonary disease, LDL-C – low density lipoprotein type C, MI – myocardial infarction, PAD – peripheral vascular disease, PCI – percutaneous intervention

Covariates included in the model	Odds ratio	95% confidence interval	p-value
Primary diagnosis (ref: CAD)			
PAD	0.50	0.36, 0.70	< 0.001
CeVD	0.24	0.15, 0.37	< 0.001
Age at index visit (ref: 60 – 70 years)			
< 60 years	1.16	1, 1.35	0.04
71 – 80 years	1.31	1.18, 1.46	< 0.001
> 80 years	0.33	0.28, 0.40	< 0.001
Self-reported Race (ref: White)			
Black	0.49	0.40, 0.60	< 0.001
Others	0.84	0.76, 0.92	< 0.001
Baseline LDL-C category (ref: LDL-C 70 – 100 mg/dl)			
100 – 130 mg/dl	2.92	2.51, 3.40	< 0.001
> 130 mg/dl	10.01	8.75, 11.46	< 0.001
Very high-risk category	1.15	1,1.32	0.03
Poly-vascular disease	1.38	1.22, 1.56	< 0.001
Ever smoked	0.93	0.85, 1.02	0.13
Hypertension	1.01	0.90, 1.13	0.81
Diabetes mellitus	1.04	0.94, 1.15	0.34
Atrial fibrillation	1.01	0.88, 1.17	0.78
COPD	0.68	0.60, 0.78	< 0.001
Heart failure	0.78	0.65, 0.93	< 0.001
Chronic kidney disease	1.15	1, 1,34	0.04
Prior MI	0.75	0.57, 0.99	0.04
Prior PCI	2.12	1.72, 2.61	< 0.001
Median annual household income (ref: < $40,000)			
$40,000 – $80,000	1.13	1.01, 1.27	0.02
> $80,000	1.41	1.14, 1.75	0.001
Community deprivation index (ref: Least deprived)			
Moderately deprived	0.87	0.77, 0.97	0.02
Most deprived	0.38	0.11, 1.20	0.1

Table 3-5. This table presents the baseline characteristics of the study cohort for patients below 75 years

*Abbreviations: CAD – coronary artery disease, CeVD – cerebrovascular disease, LDL-C – low density lipoprotein type C, MI – myocardial infarction, PAD – peripheral vascular disease, PCI – percutaneous intervention. *Standardized differences between groups (SD) > 0.1 is considered significantly different.*

	Whole Cohort (n = 290,635)	CAD Group (n = 187,107)	PAD Group (n = 46,793)	Standardized Difference* (PAD vs CAD)	CeVD Group (n = 56,735)	Standardized Difference* (CeVD vs CAD)
Age (Median [IQR]) years	69 [64, 72]	69 [64, 72]	69 [64, 72]	0.04	69 [63, 72]	0.03
Males	274,899 (94.6)	178,453 (95.4)	44072 (94.2)	0.054	52,374 (92.3)	0.128
Self-reported race				0.17		0.22
White	138,479 (47.6)	93,419 (49.9)	21,032 (44.9)		24,028 (42.4)	
Black	31,589 (10.9)	16,405 (8.8)	6,521 (13.9)		8,663 (15.3)	
Others	120,567 (41.5)	77,283 (41.3)	19,240 (41.1)		24,044 (42.4)	
Diabetes mellitus	108,762 (37.4)	62,333 (33.3)	22,076 (47.2)	0.286	24,353 (42.9)	0.199
Systemic hypertension	192,997 (66.4)	125,216 (66.9)	30,274 (64.7)	0.047	37,507 (66.1)	0.017
Heart failure	23,090 (7.9)	17,130 (9.2)	3,004 (6.4)	0.102	2,956 (5.2)	0.153
Chronic kidney disease	25,683 (8.8)	14,724 (7.9)	5,370 (11.5)	0.122	5,589 (9.9)	0.07
Atrial fibrillation	26,866 (9.2)	18,201 (9.7)	3,786 (8.1)	0.057	4,879 (8.6)	0.039
Prior MI	8,487 (2.9)	7,535 (4)	439 (0.9)	0.20	513 (0.9)	0.202
Prior PCI	6,816 (2.3)	6,318 (3.4)	249 (0.5)	0.207	249 (0.4)	0.216
COPD	51,028 (17.6)	32,623 17.4)	9,266 (19.8)	0.061	9,139 (16.1)	0.036
Poly-vascular disease	40,717 (14.0)	17,382 (9.3)	10,925 (23.3)	0.387	12,410 (21.9)	0.352
'Very high risk'	178,863 (61.5)	105,380 (56.3)	40,625 (86.8)	0.718	32,858 (57.9)	0.032

Median household income group	46,971 [38,49, 58,750]	47,308 [38,923, 5,901]	46,175[37,637, 58,183.5]	0.069	46,460 [37,853.25, 58,332]	0.052
< $40,000	81,403 (28.9)	50,716 (28.0)	14,031 (31.1)		16,656 (30.3)	
$40,000 - $80,000	181,833 (64.6)	118,631 (65.4)	28,408 (62.9)		34,794 (63.3)	
> $80,000	18,163 (6.5)	11,972 (6.6)	2,713 (6)		3,478 (6.3)	
US Region				0.06		0.062
Midwest	61,531 (21.5)	39,452 (21.4)	10,542 (22.9)		11,537 (20.6)	
Northeast	43,494 (15.2)	28,392 (15.4)	7,513 (16.3)		7,589 (13.5)	
South	129,225 (45.1)	83,021 (44.9)	20,264 (44.1)		25,940 (46.3)	
West	52,525 (18.3)	33,898 (18.3)	7,647 (16.6)		10,980 (19.6)	
Rural location	169,083 (59.5)	113,300 (61.9)	25,107 (54.8)	0.146		0.136
Baseline LDL-C levels (Median [IQR])	100[84, 125]	100 [83, 125]	103 [85, 127]	0.013	103 [85, 127]	0.064
Baseline LDL-C category (mg/dl)				0.043		0.081
70 - 100	145,310 (50.0)	95,269 (50.9)	23,433 (50.1)		26,608 (46.9)	
100 – 130	82,887 (28.5)	51,864 (27.7)	13,835 (29.6)		17,188 (30.3)	
> 130	62,438 (21.5)	39,974 (21.4)	9,525 (20.4)		12,939 (22.8)	
On statin therapy (pre-index window [-180,0] days)	170,318 (58.6)	110,987 (59.3)	27,004 (57.7)		32,327 (57)	
Statin therapy Intensity				0.167		0.139
No statins	120,317 (41.4)	76,120 (40.7)	19,789 (42.3)		24,408 (43)	
Low/moderate	86,112 (29.6)	52,433 (28)	15,636 (33.4)		18,043 (31.8)	
High	84,206 (29.0)	58,554 (31.3)	11,368 (24.3)		14,284 (25.2)	
On ezetimibe therapy (pre-index window [-180,0] days)	2,827 1.0)	2,152 (1.2)	312 (0.7)	0.051	363 (0.6)	0.054
Year of index visit				0.05		0.107
2016	131,349 (45.2)	86,990 (46.5)	20,844 (44.5)		23,515 (41.4)	

2017	64,108 (22.1)	41,030 (21.9)	10,121 (21.6)		12,957 (22.8)	
2018	50,137 (17.3)	31,291 (16.7)	8,289 (17.7)		10,557 (18.6)	
2019	45,041 (15.5)	27,796 (14.9)	7,539 (16.1)		9,706 (17.1)	
Community deprivation index (Median [IQR])	0.39 [0.33, 0.45]	0.38 [0.33, 0.44]	0.39 [0.33, 0.46	0.094	0.39 [0.33, 0.46]	0.094
Community deprivation index Tertile				0.051		0.05
I (Least deprived)	75,095 (26.1)	49,678 (26.8)	11,573 (25.2)		13,844 (24.7)	
II (Moderately deprived)	210,605 (73.3)	134,683 (72.7)	34,053 (74)		41,869 (74.7)	
III (Most deprived)	1,656 (0.6)	938 (0.5)	369 (0.8)		349 (0.6)	

Table 3-6. Sensitivity analysis by fitting models only for patients younger than 75 years

Covariates included in the model	Odds ratio	95% confidence interval	p-value
Primary diagnosis (ref: CAD)			
PAD	0.46	0.31, 0.70	< 0.001
CeVD	0.26	0.16, 0.44	< 0.001
Baseline LDL-C category (ref: LDL-C 70 – 100 mg/dl)			
100 – 130 mg/dl	2.61	2.18, 3.13	< 0.001
> 130 mg/dl	8.5	7.2, 9.9	< 0.001
Very high-risk category	1.21	1.08,1.41	0.01
Poly-vascular disease	1.39	1.19, 1.61	< 0.001
Ever smoked	0.85	0.77, 0.95	< 0.001
Hypertension	1.04	0.91, 1.18	0.63
Diabetes mellitus	0.96	0.86, 1.09	0.61
Atrial fibrillation	1.04	0.86, 1.09	0.49
COPD	0.71	0.61, 0.84	< 0.001
Heart failure	0.74	0.59, 0.92	< 0.001
Chronic kidney disease	1.29	1.08, 1.55	< 0.001
Prior MI	0.74	0.54, 1.01	0.06
Prior PCI	2.39	1.88, 3.03	< 0.001
Median annual household income (ref: < $40,000)			
$40,000 – $80,000	1.12	0.98, 1.28	0.09
> $80,000	1.53	1.19, 1.98	0.005
Community deprivation index (ref: Least deprived)			
Moderately deprived	0.90	0.78, 1.04	0.16
Most deprived	0.18	0.02, 1.30	0.09

3.4 Author declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	Disparities in PCSK9 Initiation Among US Veterans with Peripheral Arterial Disease or Cerebrovascular Disease. Deo SV, McAllister D, LaForest S, Altarabsheh S, Elgudin YE, Dunlay S, Singh S, Parikh S, Sattar N, Pell JP. Am J Cardiovasc Drugs. 2023 May;23(3):311-321. doi: 10.1007/s40256-023-00576-7. Epub 2023 Mar 22. PMID: 36947397 SVD, LAF, YE – Louis Stokes Cleveland VA Medical Center, Cleveland, USA SA, SD – Mayo Clinic, Rochester USA SP – Columbia University, New York USA SS – University of Calgary, Alberta, Canada NS, JP, DAM, SVD – University of Glasgow, Glasgow, UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	**SVD, JP,NS, DAM**
Data Curation	SVD
Formal Analysis	SVD
Investigation	SVD
Methodology	SVD,JP,NS, DAM
Project Administration	JP,NS
Visualisation	SVD
Writing - original draft	SVD
Writing - review & editing	JP,NS,YE,SLF,SA,SD,SS,SP

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 4: Paper 3

4 Lipid-lowering in ‘very high risk’ patients undergoing coronary artery bypass surgery and its projected reduction in risk for recurrent vascular events - A Monte Carlo stepwise simulation approach.

4.1 Preface

In the prior chapter, I studied the challenges faced in PCSK9i initiation for US Veterans with ASCVD. Recently introduced non-statin drugs such as PCSK9i and Inclisiran are very expensive which is a hurdle for many patients. However, before resorting to these newer agents, it is important that eligible patients first receive high-intensity statin therapy which is then supplemented with oral Ezetimibe. High-intensity statin therapy and Ezetimibe are known to reduce LDL-C levels on average by 50% and 10% respectively. In my prior chapter, I observed that only 25% and 1% ASCVD patients received high-intensity statin and Ezetimibe therapy respectively (Deo et al., 2023b). Other cohort studies have also reported very low use of Ezetimibe therapy (Dayoub et al., 2021). Therefore, in the present chapter, I report a mathematical simulation model that used a pragmatic stepwise LLT approach towards reaching recommended LDL-C levels for ASCVD patients. In this study, I was able to demonstrate that with the pragmatic use of a combination of statin and Ezetimibe therapy, the need for more expensive drugs such as PCSK9i and Inclisiran will be very low.

4.2 Published Manuscript

Citation

Lipid Lowering in "Very High Risk" Patients Undergoing Coronary Artery Bypass Surgery and Its Projected Reduction in Risk for Recurrent Vascular Events: A Monte Carlo Stepwise Simulation Approach.

Deo S, Ueda P, Sheikh AM, Altarabsheh S, Elgudin Y, Rubelowsky J, Cmolik B, Hawkins N, McAllister D, Ruel M, Sattar N, Pell J.J Cardiovasc Pharmacol. 2023 Feb 1;81(2):120-128. doi: 10.1097/FJC.0000000000001374.PMID: 36315474

Manuscript

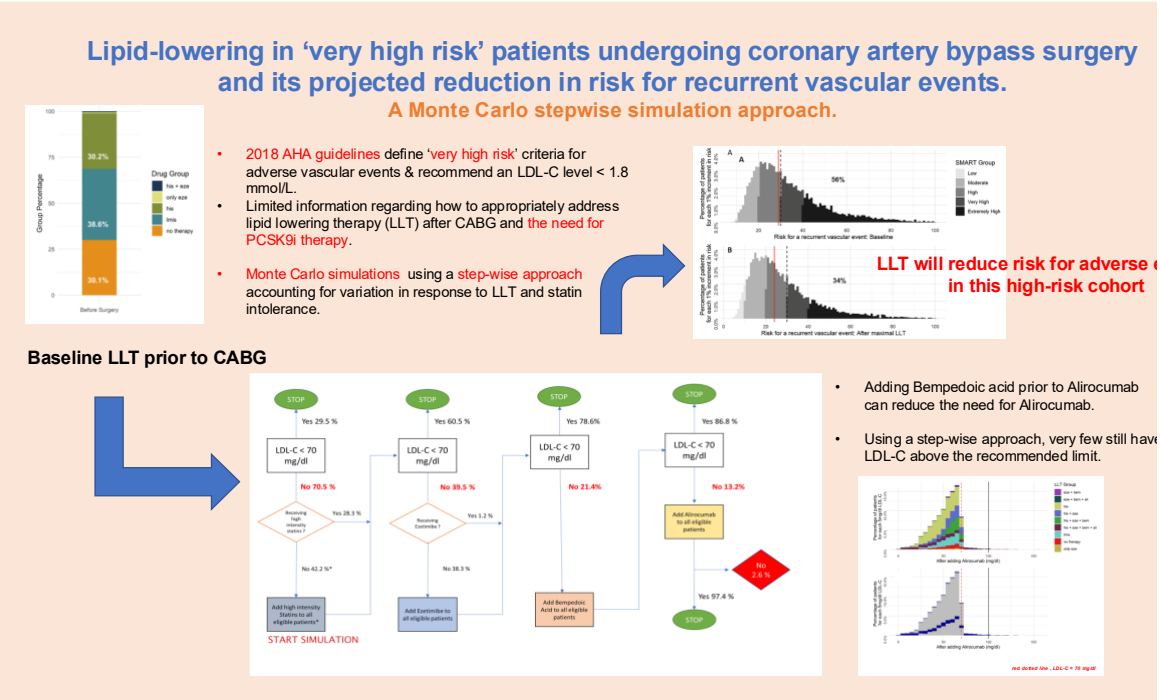

Figure 4-1. Graphical abstract of the study

ABSTRACT

2018 AHA guidelines provide criteria to identify patients at very high-risk (VHR) for adverse vascular events and recommend an LDL-C level < 1.8 mmol/L. Data regarding the 10-year risk for adverse vascular events in CABG patients at VHR and the need for non-statin therapies in the VHR cohort are limited.

We queried a national cohort of CABG patients to answer these questions. The projected reduction of LDL-C from stepwise escalation of lipid lowering therapy (LLT) was simulated; Monte Carlo methods were used to account for patient-level heterogeneity in treatment effects. Data on preoperative statin therapy and LDL-C levels were obtained. In the first scenario, all eligible patients not at

target LDL-C received high intensity statins, followed by ezetimibe and then alirocumab; alternatively, bempedoic acid was also utilized. The 10-year risk for an adverse vascular event was estimated using a validated risk score. Potential risk reduction was estimated after simulating maximal LLT. Before CABG, 8,948/27,443 patients [(median LDL-C 85 mg/dl) were VHR. In the whole cohort, 31% were receiving high intensity statins. With stepwise LLT escalation, the proportion of patients at target were 60%, 78%, 86% and 97% after high intensity statins, ezetimibe, bempedoic acid and alirocumab respectively. The projected 10-year risk to suffer a vascular event reduced by 4.6%.

A large proportion of CABG patients who are at VHR for vascular events fail to meet 2018 AHA LDL-C targets. A stepwise approach, particularly with the use of bempedoic acid, can significantly reduce the need for more expensive PCSK9 inhibitors.

INTRODUCTION

Patients undergoing coronary artery bypass grafting (CABG) often have complex multi-vessel coronary artery disease. Postoperative morbidity and mortality of patients following CABG is presently very low (Dani et al., 2021, Raza et al., 2019), but the long-term survival often depends upon freedom from recurrent adverse atherosclerotic events. In this aspect, guideline directed medical therapy (GDMT) , specifically lipid lowering therapy (LLT) forms an important component of secondary prevention after CABG (Kurlansky et al., 2016) (Kulik et al., 2015). In 2018, the American Heart Association, introduced criteria to identify patients with established atherosclerotic cardiovascular disease (ASCVD) that may have a ‘very high risk’ (VHR) for suffering a recurrent adverse vascular event (Grundy et al., 2019) (Table 4-1). The association further recommends aggressive LLT in this group of patients with the aim of lowering LDL-C < 70 mg/dl [1.8 mmol/L]. To achieve this target, after maximally tolerated statin therapy, non-statin drugs like ezetimibe (22.7% mean reduction in LDL-C reduction) and proprotein convertase subtilsin-kexin type 9 inhibitors (PCSK-9i) (48.6% mean LDL-C reduction) are recommended (Cannon et al., 2017).

However, cost (at the healthcare system and patient level) remains a very important practical limitation to the widespread use of PCSK9i (Arrieta et al., 2017). Therefore, further stratification of these very high patients may help by identifying those that are truly at a prohibitively high risk. The SMART (Secondary Manifestations of Arterial disease) score, is one such score, as it can predict the 10-year vascular event rate among patients with established ASCVD, and stratify patients into groups according to their risk probability (Dorresteijn et al., 2013) (Kaasenbrood et al., 2016)(Table 4-2).

The Monte Carlo simulation approach is a practical tool which can be used to project changes in baseline values under certain specified conditions. Advantage of this approach is the ability to incorporate epistemic and aleatoric uncertainty. Prior simulation studies evaluating the need for non-statin therapies in ASCVD patients exist (Allahyari et al., 2020) (Koskinas et al., 2021). However, most have applied the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines(Allahyari et al., 2020, Koskinas et al., 2021). Significant differences exist between the 2018 AHA/ACC and 2019 ESC/EAS guidelines. The 2 guidelines differ in their criteria to determine VHR patients as well as their recommended LDL-C targets (Grundy et al., 2019) (Mach et al., 2020). Moreover, limited information exists regarding the potential beneficial effect that appropriate stepwise LLT intensification may have on the risk of having a recurrent adverse vascular event in this very high cohort. Using a Monte Carlo simulation approach, we evaluated the LDL-C lowering possibility with a stepwise escalation in lipid lowering therapy.

Our aims were to:

(1) Obtain the 10-year projected risk of suffering an adverse vascular event in a ‘very high risk’ cohort of CABG patients.

(2) Simulate a stepwise intensification of LLT to understand the need for PCSK9i according to the 2018 AHA criteria when, more specifically, bempedoic acid is administered prior to PCSK9i therapy; and

(3) Estimate the absolute risk reduction and residual risk of an adverse vascular event that may be obtained with the stepwise LLT simulation.

METHODS

The Veteran Health Affairs is largest integrated health care system in the United States, providing care to approximately 9 million Veterans (Administration, 2021a). The VA Surgical Quality Initiative Project (VASQIP), the primary source for this study, contains perioperative clinical information regarding patients that receive surgery in the VA system. Laboratory results, clinical characteristics and preoperative prescription information can be obtained from other data sources within the central computing infrastructure and linked together for each patient. The study was approved by the Louis Stokes Cleveland VAMC institutional review committee: IRB# CY-045 and individual patient consent was waived.

From patients that underwent CABG (January 2010 – September 2019) we initially identified 27,443 who received primary isolated CABG and had a non-missing LDL-C level prior to surgery. Among these, 8,948 (32.6%) patients that were defined as very high-risk according to the 2018 AHA/ACC criteria were the subject of this study (Figure 4-2). Demographics like age, sex, self-reported race and preoperative clinical characteristics for all patients were obtained. The International Classification of Diseases, 9th and 10th edition codes were used to identify clinical comorbidities when these were not directly available from the database.

Ongoing LLT was defined as a prescription fill within 120 days prior to the surgery. Patients were defined as not receiving any LLT if they did not have a documented prescription for a statin, ezetimibe or PCSK9i drug within 120 days of surgery. Using the type and dose of statin therapy and the AHA/ACC guidelines on statin dosing, statin therapy was classified as either low/moderate or high intensity(Chou R).

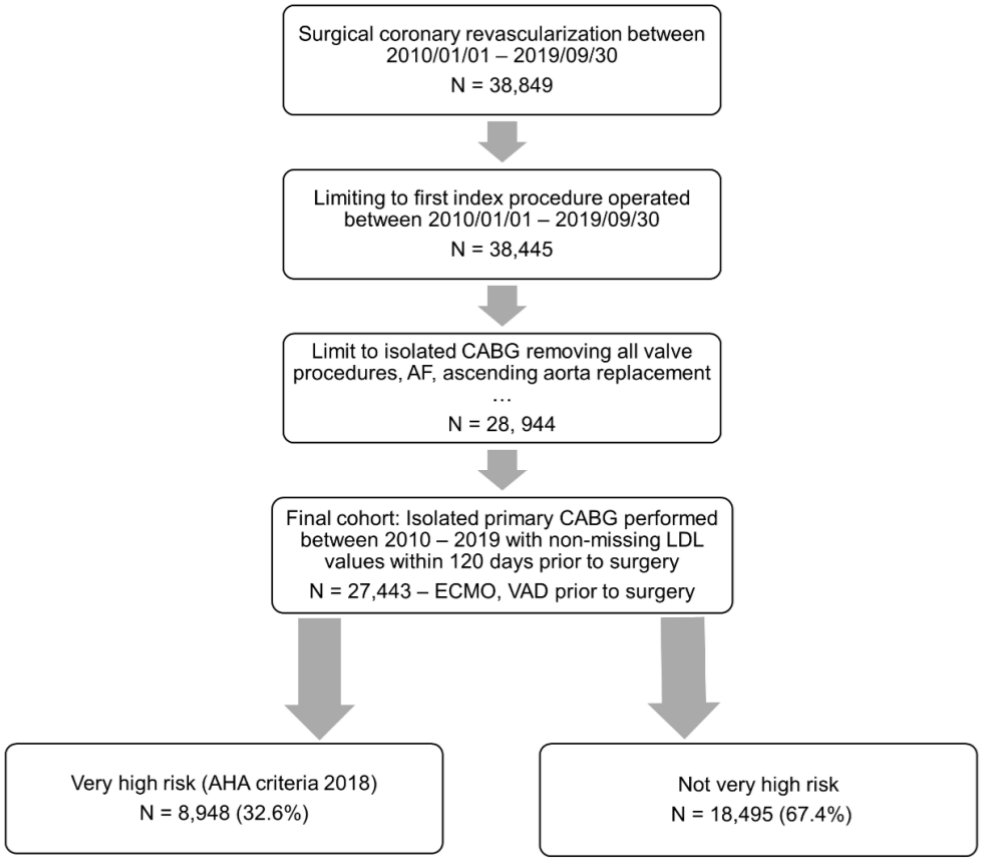

Figure 4-2. Flowchart of the cohort selection process for this study

This flowchart depicts the cohort selection process. From 38,849 patients (January 2010 - September 2019, 41 VA medical centers in the US) that had CABG, we initially limited our cohort to patients that had isolated CABG. Therefore, patients that underwent concomitant ascending aorta replacement, valvular heart surgery or other major procedures were excluded. We further excluded patients with missing LDL-C values within 120 days prior to surgery, and then selected patients defined as 'very high risk (VHR)' for a recurrent vascular event.

Based on their LLT prior to CABG, patients were grouped as follows: (1) no LLT (2) low or moderate intensity statin therapy (3) high intensity statin therapy (4) high intensity statins + ezetimibe therapy and (5) only ezetimibe therapy. None were receiving PCSK9i therapy prior to surgery.

The LDL-C level within 120 days prior to the surgical procedure was also obtained. When multiple results were available, the result closest to the surgery

date was chosen. For patients that were not on LLT, these readings were their untreated LDL-C levels. For patients receiving LLT at the time of surgery, untreated LDL-C levels were calculated using the extrapolation methods recommended by the ESC / EAS (Allahyari et al., 2020). At each step in the simulation pathway, the LDL-C from the prior step and the expected reduction in LDL-C, modelled as a ß distribution, were used to obtain the new projected LDL-C level. The ß distribution for the projected LDL-C reduction for each LLT was calculated using data provided by Cannon et al. (Cannon et al., 2017) (Table 4-3). These values have been implemented and validated in prior analyses (Allahyari et al., 2020, Koskinas et al., 2021).

Data Analyses:

LLT escalation was simulated in a stepwise manner. For each step, a Monte Carlo model was run (with 10,000 simulations) to simulate the heterogeneity in the projected LDL-C reduction. To model high-intensity statin therapy, rosuvastatin 40mg was used, as among statins, this therapy provides the maximal LDL-C reduction (Cannon et al., 2017). Among available PCSK9 inhibitors,–alirocumab 75mg biweekly, was chosen to model the simulation as, alirocumab is the PCSK9i of choice in the VA healthcare system. At each step, the proportion of patients with LDL-C < 70 mg/dl [1.8 mmol/L] i.e., at target were calculated. The 95% confidence intervals for these target proportions were obtained by non-parametric bootstrap. Patients above target entered the next step of LLT intensification. Statin intolerance among statin naïve was modelled at 15%.

The following scenarios were simulated:

(1) Baseline scenario: In this scenario, all eligible patients with LDL-C > 70 mg/dl [1.8 mol/L] prior to surgery and not on high intensity statin therapy, were simulated to receive high intensity statin therapy. Statin intolerance (15%) was accounted for in this model. After high intensity statin therapy, patients received 10 mg ezetimibe, and finally, those that still had LDL-C levels > 70 mg/dl [1.8 mmol/L] were simulated to receive 75mg biweekly alirocumab.

(2) Adding bempedoic acid prior to alirocumab: In this situation, after adding high intensity statins and ezetimibe, 180 mg bempedoic acid was simulated in patients with LDL-C > 70 mg/dl [1.8 mmol/L]. Alirocumab 75mg biweekly was then added as the final step in this pathway.

Coefficients for each variable included in the SMART score were obtained from the appendix of the manuscript outlining model development (Dorresteijn et al., 2013). The clinical SMART score contains the following variables – age, sex, smoking status, systolic blood pressure, presence of diabetes mellitus, coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm, years since diagnosis of ASCVD, total cholesterol (mmol/lit), HDL-cholesterol (mmol/lit), eGFR (ml/min/m^2) and hs-CRP (mg/dl). Information regarding years since diagnosis of ASCVD, systolic blood pressure and hs-CRP were not available in our database. Hence, these values were imputed by using a random sampling algorithm from the summary statistics presented in the SMART score manuscript (Dorresteijn et al., 2013). Missing data was present for total cholesterol (10%) and HDL-cholesterol (9%). Mean imputation was used to fill missing information. All other variables used in the model were complete. In a large individual patient level meta-analysis, the Cholesterol Treatment Trialists (CTT) collaborators reported a 12% risk reduction per 1 mmol/L of LDL-C change(Baigent et al., 2005). Therefore, using the simulated mmol/ lit LDL-C reduction, a projected hazard ratio was calculated for each patient. The logarithm of this hazard ratio was then included in the SMART regression model and the projected residual risk for an adverse vascular event at 10 years was calculated for that individual was calculated (Table 4-4).

Statistical analyses were performed using R 4.0.2 (The R Foundation for Statistical Computing, Austria). Statistical code is available at the corresponding authors Github account (https://github.com/svd09). The appendix contains further information regarding statistical analyses performed.

RESULTS

We studied 8,948 patients (January 2010 – September 2019) undergoing CABG and identified as very high risk as per the 2018 AHA/ACC criteria. In this very high-risk cohort, 2,408 (27%) were included as they had at least 2 major criteria, while all other patients had at least 1 major and 2 minor criteria. The median age of the very high-risk cohort was 66 (IQR: 62 – 71) years and 948/8,948 (11.1%) were >70 years old at surgery. The prevalence of diabetes mellitus, hypertension, and peripheral vascular disease was 49%, 94% and 58% respectively (Table 4-5)

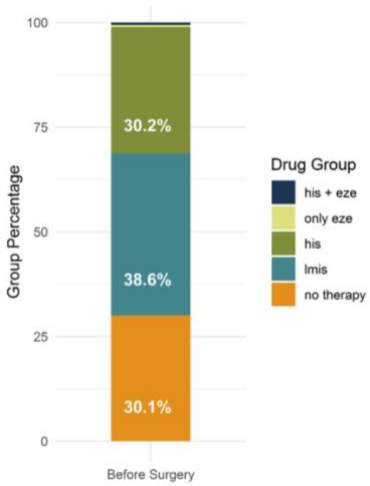

Figure 4-3. LLT therapy prior to CABG

Prior to CABG, 30 % were not on LLT, while 30 % and 39 % were receiving high-intensity and low/moderate intensity statin therapy respectively. Abbreviations: eze - ezetimibe, lmis - low/moderate intensity statin therapy, his - high intensity statin therapy

Preoperatively, the median LDL-C level was 86 (66 – 115) mg/dl [2.2 (IQR: 1.7 – 2.9) mmol/L]. LDL-C < 70 mg/dl [1.8 mmol/L], 70 – 100 mg/dl [1.8 – 2.6 mmol/L] and > 100 mg/dl [2.6 mmol/L] were present in 29%, 37% and 34% respectively. Prior to surgery, in the very high-risk group, 70% were receiving LLT; 40% and 30% were receiving low/moderate intensity statin and high intensity statin therapy respectively (Figure 4-3). Only 1% of patients were receiving ezetimibe therapy prior to surgery. Compared to patients not on LLT, those receiving LLT had a significantly lower median LDL-C level (81 vs 103 mg/dl; p < 0.001) [2 vs 2.6 mmol/L].

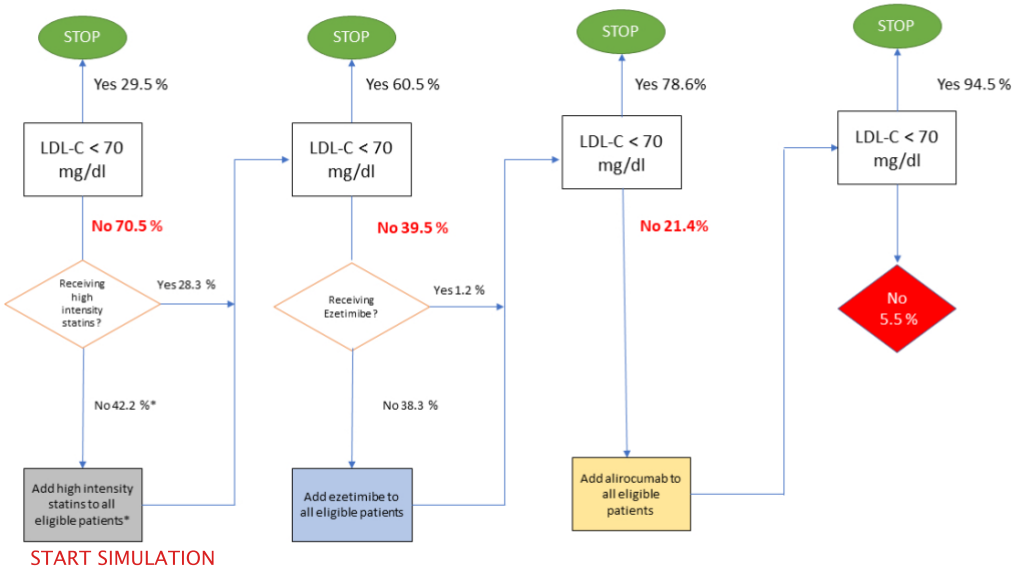

Figure 4-4. Flowchart of the stepwise simulation

Flowchart of the stepwise simulated escalation of LLT to achieve a target LDL-C level < 1.8 mmol/lit (70 mg/dl). * High intensity statin modeled is Rosuvastatin 40 mg

Prior to surgery, from the LDL-C levels observed in our data, 29.5% (95% CI: 28.6 – 30.5%) of patients had an LDL-C < 70 mg/dl [1.8 mmol/L]. The remaining 70.5% were, therefore, eligible for a stepwise intensification of their LLT (S-table 4). Among statin-naïve patients, those simulated as statin intolerant did not receive any statin therapy. The remaining patients were simulated to receive 40mg rosuvastatin 40 mg. After adding rosuvastatin therapy, the overall anticipated median LDL-C for the entire cohort will be 64 (IQR: 48, 87) mg/dl [1.6 (IQR: 1.2, 2.2) mmol/L]. At the end of this step, 77%, 13%, and 1% will be receiving high intensity statins, moderate/low intensity statin, and ezetimibe therapy respectively. After simulating treatment with 10 mg ezetimibe for those patients with LDL-C > 70 mg/dl [1.8 mmol/L], 76.1% are expected to attain target. The overall estimated LDL-C will now reduce to a median level of 59 (IQR: 46 – 69) mg/dl [1.5 (IQR: 1.2, 1.7) mmol/L]. In this simulation, after rosuvastatin and ezetimibe therapy, 23.9% of patients will still be projected to be above target LDL-C; they were therefore simulated to receive 75mg biweekly alirocumab. At the end of this simulation, from the whole cohort, we expect 94% to attain the

target LDL-C. (Figure 4-4). Overall, in this simulated scenario, 41% received only high intensity statins. Ezetimibe and alirocumab therapy were added in 15% and 21% patients respectively (Figure 4-5).

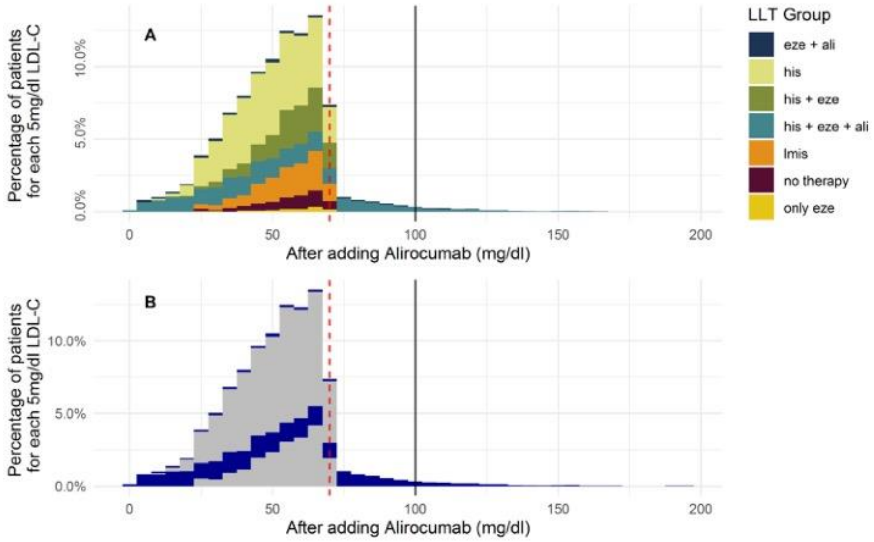

Figure 4-5. Projected LDL-C at the end of simulation

A) Distribution of projected LDL-C levels at the end of the simulation algorithm in the prior figure. (B) After complete simulation, proportion of patients requiring 75mg bi-weekly alirocumab to attain LDL-C levels < 1.8 mmol/Lit is depicted in blue. Abbreviations: ali – alirocumab, eze – ezetimibe, lmis – low/moderate intensity statin therapy, his – high intensity statin therapy

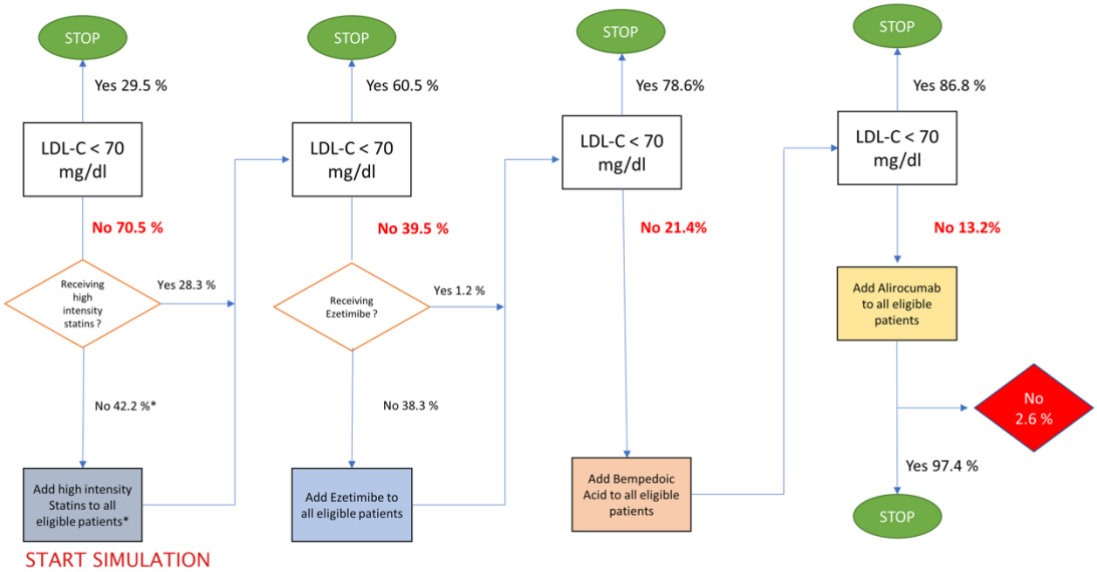

Figure 4-6. Flowchart of the simulation adding Bempedoic Acid

Flowchart of the stepwise simulated escalation of LLT to achieve a target LDL-C level < 1.8 mmol/lit (70 mg/dl). * High intensity statin modeled is Rosuvastatin 40 mg

In the second scenario (Figure 4-6), after the initial steps of simulating 40mg rosuvastatin and 10mg ezetimibe therapy, 180mg bempedoic acid was added to those not reaching the target LDL-C level. Therefore, 21.4% of patients were simulated to receive 180mg bempedoic acid. After this step, we project the median LDL-C concentration will be 57 (IQR: 46 – 66) mg/dl [1.4 (IQR: 1.2, 1.7) mmol/L] and the percentage of patients expected to reach the target will increase from 78.6% to 86.8%. In this scenario, after simulating treatment with 75mg biweekly alirocumab, we expect that 97.4% patients will reach the target (Figure 4-6). Overall, in this scenario, 42% and 14% received high intensity and low/moderate intensity statins respectively; however, 21% were projected to need triple drug therapy with rosuvastatin, ezetimibe and bempedoic acid (Figure 4-7)(Table 4-6).

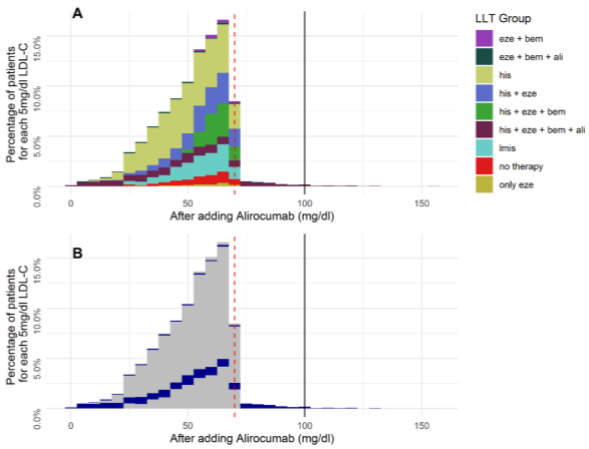

Figure 4-7. Projected LDL-C levels after adding Bempedoic Acid

(A) Distribution of projected LDL-C levels at the end of the simulation algorithm in prior figure. (B) After complete simulation, proportion of patients requiring 75mg bi-weekly alirocumab to attain LDL-C levels < 1.8 mmol/Lit is depicted in blue. Abbreviations: ali - alirocumab, bem - bempedoic acid, eze - ezetimibe, lmis - low/moderate intensity statin therapy, his - high intensity statin therapy

Compared to patients in the derivation of the SMART study cohort, our patients were older, with a higher prevalence of peripheral vascular disease. The prevalence of diabetes mellitus was higher in our cohort, while the rate of active smoking was comparable. Preoperatively, the median 10-year risk was 29% (IQR: 21% – 40%) (Figure 4-8). Overall, 56% of patients were in the very high (30% to < 40%) or extremely high-risk category (> 40%), while 19% were in the low (< 10%) or moderate (10% to < 20%) risk category. After simulating maximal LLT and calculating the projected LDL-C levels, we can anticipate that the proportion of patients in the low or moderate risk category may increase from 19% to 36%, while those in the very high or extremely high-risk category may reduce from 56% to 34%. We project that, with a maximal LLT, in our cohort, we may observe a median absolute risk reduction of 4.6 % (IQR: 0.1% - 8.2%). However, even after maximal LLT, we estimate that the median residual risk in our cohort for suffering an adverse vascular event over 10 years will be 23.9 % (16.7% – 34.7%).

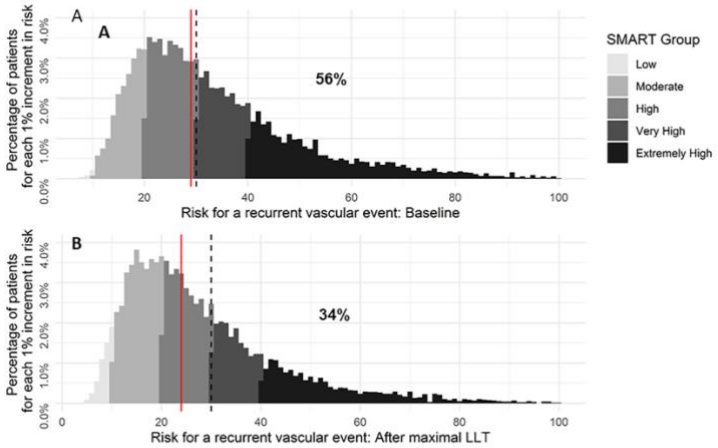

Figure 4-8. SMART scores at baseline and after LLT simulation

A histogram of SMART scores from our cohort at baseline (A) and then after simulating treatment with maximal LLT (B). After simulating treatment with maximal LLT, the percentage of patients in the very high risk (SMART score: 30 – 40%) and extremely high risk (SMART score > 40%) reduced from 56% to 34%. The median SMART score (red line) correspondingly reduced from 29% to 24%. Red line – median SMART score, black dotted line – SMART score of 30%.

DISCUSSION

The 2018 guidelines from the AHA/ACC recommend that patients at 'very high risk' of suffering an adverse vascular event receive intensified LLT to achieve a target LDL-C concentration < 70 mg/dl [1.8 mmol/L]; in many patients, this cut-off is challenging to achieve using only statins. They, therefore, recommend an incremental approach of high intensity statins followed by non-statin drugs like ezetimibe and PCSK9i. We observed that, in a nationally representative cohort of CABG patients, almost one-third fit the 2018 AHA/ACC criteria of 'very high risk'. Simulating a stepwise approach to LLT intensification and Monte Carlo methods to model the heterogeneity in treatment effects, we project that, in our cohort, 24% of patients would need incremental alirocumab therapy to reach the recommended target LDL-C. After treating with maximally tolerated statin therapy and ezetimibe therapy, however, if 180mg bempedoic acid were added, this may reduce the need for PCSK9i therapy by almost 8%. In patients deemed

to be ‘very high risk’ by the 2018 AHA/ACC criteria, we observed a wide range of SMART scores. In fact, according to the SMART model, 1/5th patients were in the low- risk category. If all patients were to receive maximally tolerated LLT, we project a 5% median absolute reduction in patients SMART scores. However, even with this simulated maximal reduction in LDL-C levels, we still project a substantial residual risk for adverse vascular events in our cohort.

In our cohort of CABG patients, approximately 30% was identified as VHR according to the 2018 AHA criteria. The incidence of VHR ranges between approximately 50 – 60% in prior studies(Colantonio et al., 2019) (An et al., 2020), while 57% and 64% from the REACH and SMART fit the ‘very high risk’ criteria (van den Berg et al., 2017). The lower incidence of VHR observed in our data could be as our cohort consists of only male CABG patients, which may introduce a selection bias. A recent study reported that the 2018 AHA/ACC criteria, themselves, have a poor discriminative ability in identifying patients at ‘true’ high risk for atherosclerotic vascular disease (van den Berg et al., 2017). However, our study and many others clearly demonstrate that targeted lipid lowering therapy is not being used by many high-risk patients. In our group, approximately 30% patients were not receiving any LLT. From those receiving any LLT, only 44% were on high intensity statin therapy (Table 1). In a cohort of privately insured patients, Colantonio et al. observed that 80% were receiving statin therapy; however, only 35% were on high intensity statin dosing (Colantonio et al., 2019). An et al. reported similar findings, with high intensity statins being prescribed in 21 – 34% patients in the VHR cohort (An et al., 2020). In the SMART and REACH registries, 66% and 70% of patients respectively were receiving statin therapy. In a cohort of patients from Sweden, among 25,466 patients with myocardial infarction, only 20% of patients prior to admission were receiving LLT, while 85% were subsequently discharged with LLT. Other studies also report high rates of needing PCSK9i therapy to meet the 2019 ESC/EAS lipid guidelines(Allahyari et al., 2020) (Koskinas et al., 2021). In our simulation, there would be a reduction in the need for PCSK9i by 8 – 10% by using bempedoic acid after ezetimibe therapy. Till date, bempedoic acid has been studied in phase 3 trials on patients with ASCVD and had demonstrated substantial reduction in

LDL-C concentrations over a 52 week period (Ray et al., 2019) (Ballantyne et al., 2020) (Goldberg et al., 2019). However, a trial examining cardiovascular outcomes with bempedoic acid therapy is ongoing (Medicine). The annual cost of bempedoic acid therapy in Germany is € 1722.50 (Blaum et al., 2021), which is less than half the cost of alirocumab therapy. Therefore, the potential use of bempedoic acid may provide a more cost-effective way of reducing LDL-C levels in very high-risk patients. Therefore, our study demonstrates that the prior use of bempedoic acid may provide financial savings to both the patient and healthcare system.

Although all patients in our cohort were deemed very high risk by the 2018 AHA/ACC criteria, using the SMART score, we still observed a wide range of estimated 10-year risk rates (Table 2). Van den Berg et al. reported that the discriminatory ability of the 2018 AHA/ACC criteria to determine a recurrent vascular event is limited (van den Berg et al., 2017). When the 2018 AHA/ACC criteria were externally validated in the REACH and SMART cohorts, the c-statistic observed was 0.53 and 0.54 respectively (van den Berg et al., 2017), suggesting minimal discriminatory ability. In our cohort of very high-risk patients, the 10-year risk of recurrent events was < 30% in half the patients. Studies have demonstrated that, at least in the United States, at present, the widespread use of PCSK9i drugs is not generally cost effective (Kazi et al., 2017). Therefore, along with the 2018 AHA criteria, we recommend physicians use a scoring system which may provide improved risk stratification. This would allow a more targeted and cost-effective approach, wherein, costly non statin drugs can be preferentially prescribed to patients at highest risk for future adverse vascular events.

The strengths of this study are the use of a large national cohort of CABG patients, reflecting a varied population, modeling the heterogeneity in the individual response to LLT with Monte Carlo methods, reliable data regarding baseline LDL-C concentrations and the availability of accurate information regarding statin therapy prior to surgery. Our study also has some limitations. As our data are from the Veteran Affairs healthcare system, patients are almost all

males. This limits generalizability of our results to women. In the calculation of the SMART score, missing data were imputed. However, we performed sensitivity analyses to evaluate the impact of such simulations on the overall results.

In conclusion, from a national database, we observed that a sizeable proportion of CABG patients fit the 2018 AHA/ACC very high-risk criteria. Lipid lowering therapy remains suboptimal with many patients having LDL-C concentrations > 70 mg/dl, the recommended target for such high-risk patients. The simulated need for PCSK9 inhibitor therapy was substantial at 21%; however, this can be reduced by 8% using bempedoic acid, emphasizing the increasing need for use of multiple lipid-lowering drugs in many patients with prior CABG. We further observed that, in our cohort, simulating maximal lipid lowering therapy may reduce the risk of recurrent events by approximately 5% from baseline. Finally, applying a well validated scoring model to our cohort, we observed a wide variation in the estimated risk rate for recurrent vascular events, suggesting a need to re-evaluate the approach to identifying high risk patients advocated by the 2018 AHA/ACC guidelines.

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4.3 Appendix

Table 4-1. Very High-Risk Criteria

This table presents the major and minor criteria to define ASCVD patients as very high risk. Patients that have 1 major + 2 minor criteria OR 2 major criteria fit the AHA 'Very high-risk' definition.

Major Criteria	Prevalence in our cohort (N = 8,948)
Recent acute coronary syndrome (within the past 12 months)	3,641 (40)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)	2,831 (31)
History of ischemic stroke	24 (0.02)
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)	5,198 (58)
Minor Criteria	
Age >_65 years	5,160 (57)
Heterozygous familial hypercholesterolemia	108 (0.01)
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)	8,948 (100)
Diabetes Mellitus	4,377 (48)
Hypertension	8,393 (93)
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m2)	2,360 (26)
Current smoking	2,781 (31)
Persistently elevated LDL-C (LDL-C >100 mg/dL (> 2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe	3,327 (37)
History of congestive heart failure	273 (3)

Table 4-2. SMART score

This table presents the criteria used to calculate the SMART score.

Risk factors included in the SMART score	Summary statistics in the SMART score derivation cohort (N = 3,489)	Summary statistics in our study cohort (N = 8,948)
Age (years)	60 (53–68)	66(62 – 71*)
Location of vascular disease		
Cerebrovascular disease	846 (27)	2,780 (31)
Coronary artery disease	1892 (60)	8,948 (100%)
Peripheral arterial disease	691 (22)	5,198 (58)
Abdominal aortic aneurysm	291 (9)	205 (0.02)
Current smoking	1169 (34)	2,781 (31)
Diabetes mellitus	592 (17)	4,377 (48)
Total cholesterol (mmol/l*)	4.9 (4.1–5.7)	4.2(3.4 – 4.7*#)
HDL-cholesterol (mmol/l**)	1.2 (1.0–1.4)	1(0.8 – 1.1*#)

Table 4-3. Projected percentage reduction according to statin dose

The change in LDL-C levels was simulated using the LDL-C at the start of each step and the estimated proportional reduction in LDL-C for simulated treatment. To simulate the proportional reduction in LDL-C levels, values were generated using a B distribution for the simulated treatment. Monte Carlo methods were used to introduce inter-individual variation in the proportional change in LDL-C levels and 10,000 random iterations were performed. Data regarding LDL-C reduction for Bempedoic acid treatment was obtained from Cicero et al.

Lipid lowering drug	Drug dose	Mean change	SD
Atorvastatin	10 mg	35.5%	10.6%
	20 mg	41.4%	13.5%
	40 mg	46.2%	12.5%
	80 mg	50.2%	13.8%
Fluvastatin*	40 mg	23.0%	10.0%
Lovastatin	10 mg	21.0%	10.1%
	20 mg	24.0%	11.0%
	40 mg	30.0%	11.0%
	60 mg	34.5%	11.7%
Pravastatin	10 mg	20.0%	11.0%
	20 mg	24.0%	11.0%
	40 mg	30.0%	13.0%
	80 mg	33.0%	11.2%
Rosuvastatin	5 mg	38.8%	13.2%
	10 mg	44.1%	12.5%
	20 mg	49.5%	13.3%
	40 mg	54.7%	12.9%
Simvastatin	5 mg	23.0%	11.0%
	10 mg	27.4%	13.7%
	20 mg	33.0%	10.4%
	40 mg	38.9%	14.0%
	80 mg	45.0%	11.7%
Ezetimibe	10 mg	22.7%	16.3%
Alirocumab	75 mg (biweekly)	48.6%	25.0%
Bempedoic Acid	180 mg	22.9%	8.04%

Table 4-4. Calculation of the SMART score

The baseline SMART score (prior to surgery) for each patient was calculated using the regression equation provided in the manuscript by Dorresteijn et al. The SMART score was created by fitting a multivariable Cox proportional hazards model. Therefore,

10-year cardiovascular disease risk (%) = (1- 0.81066 exp[A + 2.099]) x 100%, where

A = -0.0850 x age in years + 0.00105 x (age in years)2 + 0.156 [if male] + 0.262 [if current smoker] + 0.00429 x systolic blood pressure in mmHg + 0.223 [if diabetic] + 0.140 [if history of coronary artery disease] + 0.406 [if history of cerebrovascular disease] + 0.558 [if abdominal aortic aneurysm] + 0.283 [if peripheral artery disease] + 0.0229 x years since first diagnosis of vascular disease - 0.426 x HDL-cholesterol in mmol/L + 0.0959 x total cholesterol in mmol/L - 0.0532 x eGFR in mL/min/1.73m^2 + 0.000306 x (eGFR in mL/min/1.73m^2)2 + 0.139 x log(hs-CRP in mg/dL).

This equation provides the SMART score for each patient prior to simulation.
Steps to calculate the SMART score after maximal LLT simulation:
Baigent et al[5], from a large individual patient level meta-analysis including 90,056 individuals in 14 randomized trials trials report that each 1 mmol/lit reduction in LDL-C reduces the risk of major vascular event by 21% i.e., hazard ratio (HR) = 0.79 for every 1 mmol/lit reduction in LDL-C. After maximal lipid lowering therapy (LLT) was simulated, the new estimated LDL-C was calculated for each patient and the difference in LDL-C (ΔLDL-C) was obtained. Using the ΔLDL-C value in mmol/lit (1 mg/dl = 0.0259 mmol/L), the hazard ratio was calculated for each patient as:
HR for ΔLDL-C = 0.79^(ΔLDL-C)
This HR was then included in the SMART score model as follows:
Revised 10-year cardiovascular disease risk (%) = (1- 0.81066 exp[A + 2.099 + log(HR for ΔLDL-C]) x 100%, where,

A = -0.0850 x age in years + 0.00105 x (age in years)2 + 0.156 [if male] + 0.262 [if current smoker] + 0.00429 x systolic blood pressure in mmHg + 0.223 [if diabetic] + 0.140 [if history of coronary artery disease] + 0.406 [if history of cerebrovascular disease] + 0.558 [if abdominal aortic aneurysm] + 0.283 [if peripheral artery disease] + 0.0229 x years since first diagnosis of vascular disease - 0.426 x HDL-cholesterol in mmol/L + 0.0959 x total cholesterol in mmol/L - 0.0532 x eGFR in mL/min/1.73m^2 + 0.000306 x (eGFR in mL/min/1.73m^2)2 + 0.139 x log(hs-CRP in mg/dL).

Table 4-5. Baseline characteristics of the study cohort

	Very high-risk cohort (N = 8,948)
Age (years)*	66 [62, 71]
Age group	
< 50	265 (3)
50 - 75	7687 (85.9)
> 75	996 (11.1)
Female	111 (1.2)
Diabetes mellitus	
No	4571 (51.1)
Medically treated DM	1529 (17.1)
Insulin treated DM	2848 (31.8)
Haemoglobin	13.3 [11.9, 14.4]
HBA1C	6.3 [5.7, 7.6]
Recent LDL (mg/dl) *	86 [66, 115]
Recent ACS	1664 (18.6)
Race	
White	6645 (74.3)
African American	994 (11.1)
Others	1309 (14.6)
Preoperative LVEF*	50 [40, 55] %
eGFR*	77 [60, 92]
Obese (BMI > 30 kg/m^2)	3791 (42.4)
Chronic AF	1039 (11.6)
CKD (eGFR < 60 ml/min/m^2)	2360 (26.4)
Active smoker	2781 (31.1)
Prior CABG	117 (1.3)
Statin therapy prior to CABG	
High intensity	2755 (30.8)
Moderate intensity	2391 (26.7)
Low intensity	1067 (11.9)
None	2735 (30.6)
Ezetimibe therapy prior to CABG	127 (1.4)
No lipid lowering therapy prior to CABG	2688 (30)
PCSK9 therapy prior to CABG	4 (0)
Preoperative LDL > 70 mg/dl	6213 (69.4)
Preoperative LDL	
<70 (< 1.8 mmol/lit)	2642 (29.5)
70 – 100 (1.6 – 2.6 mmol/lit)	2997 (33.5)
> 100 (> 2.6 mmol/lit)	3309 (37.0)

Table 4-6. Percentage of patients meeting LDL-C target at the end of simulation

*This table presents the percentage of patients meeting target LDL-C < 70 mg/dl after each step of the two simulated scenarios. Scenario 1 consists of baseline – high intensity statin therapy (rosuvastatin 40 mg)– ezetimibe 10 mg – alirocumab 75mg bi-weekly. Scenario 2 consists of baseline – high intensity statins (rosuvastatin 40 mg) – ezetimibe 10 mg – bempedoic acid 180 mg – alirocumab 75mg bi-weekly. *PCSK9i used is 75mg Alirocumab biweekly, as that is the PCSK9i preferred by the VA Pharmacy Management Program. # Confidence intervals were obtained with bootstrap simulations (n = 10,000).*

Scenario	Simulation Step	Proportion at target LDL-C at the end of that simulation[#]
Scenario 1	Baseline	29.5 (28.6, 30.5) %
	Add 40 mg Rosuvastatin to all eligible patients	60.5 (59.5, 61.5) %
	Add Ezetimibe to all eligible patients	76.1 (75.2, 77) %
	Add Alirocumab to all eligible patients*	94.2 (93.7, 94.6) %
Scenario 2	Baseline	29.5 (28.6, 30.5) %
	Add 40 mg Rosuvastatin to all eligible patients	60.5 (59.5, 61.5) %
	Add 10 mg Ezetimibe to all eligible patients	76.1 (75.2, 77) %
	Add 180 mg Bempedoic acid to all eligible patients	86.8 (86, 87.5) %
	Add Alirocumab to all eligible patients*	97.4 (97.1, 97.7) %

4.4 Author Declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	Lipid Lowering in 'Very High Risk' Patients undergoing Coronary Artery Bypass Surgery and its Projected Reduction in Risk for Recurrent Vascular Events: A Monte Carlo Stepwise Simulation Approach Deo S, Ueda P, Sheikh AM, Altarabsheh S, Elgudin Y, Rubelowsky J, Cmolik B, Hawkins N, McAllister D, Ruel M, Sattar N, Pell J.J Cardiovasc Pharmacol. 2023 Feb 1;81(2):120-128. doi: 10.1097/FJC.0000000000001374.PMID: 36315474 SVD, YE, JR, BC – Louis Stokes Cleveland VA Medical Center, Cleveland USA PU – Karolikska Institutet, Stockholm, Sweden AMS – Southern Illinois School of Medicine, Springfield,USA MR – Ottawa Heart Institute, Ottawa,Canada DAM, NS, JP, NH, SVD – University of Glasgow, Glasgow UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	SVD, JP, NS,NH, DMA
Data Curation	SD
Formal Analysis	SD
Investigation	SD
Methodology	SD,PU, JP,NS, NH, DMA
Project Administration	JP,NS
Visualisation	SD
Writing - original draft	SD, AMS
Writing - review & editing	JP,NS,YE, BC, DMA, NH,

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 5: Paper 4

5 Validating the SMART2 score in a racially diverse high-risk nationwide cohort of patients receiving coronary artery bypass grafting

5.1 Preface

Patients that need CABG often have complex, multivessel disease and a large proportion of them also have significant comorbidities. However, despite this, in my prior chapters, I have reported that a large majority of them are not receiving guideline directed medical therapy to prevent recurrent major adverse cardiovascular events. In Chapters 2 and 3, I elucidated some factors that influenced non-uptake of some GDMT drugs. Among those, an important observation from Chapter 3 was the substantial variation in PCSK9i initiation across VA medical centres. This demonstrated that deciding appropriate therapies after surgery is dependent upon a shared decision-making process between healthcare provider and patient. Important to this discussion is the estimation and projection of the potential risk for future MACE as such risk stratification may aid decision making. The Society of Thoracic Surgeons have developed a risk prediction calculator (*https://sts.org*) that is routinely used clinically in the US while the European Society for Cardiothoracic Surgery recommends using the EUROSCORE II; both these risk calculators predict early (in-hospital or 30-day) post-operative outcomes. Other published risk prediction models also predict either short-term or long-term mortality (Parolari et al., 2009, Ma et al., 2017, Choi et al., 2021). However, deciding the correct secondary preventive therapies is dependent upon reliably predicting the mid- and long-term risk for recurrent MACE events, for which, no calculators exist for use in CABG patients. In fact, while the American Heart Association has routinely supported the use of the Framingham Score in the past, and now recommends using the PREVENT score, to predict 10-year incident cardiovascular disease, they do not support any risk prediction model to estimate the risk for recurrent MACE in people with established cardiovascular disease. The European Society of Cardiology supports using the Secondary Manifestations of Arterial Disease

(SMART2) risk score for the estimation of 10-year recurrent MACE risk (*https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score*) in patients with stable ASCVD. While this score can potentially be used for the estimation of recurrent MACE risk in patients' post-CABG, such a validation has not yet been performed. Hence, given the lack of scores suitable for evaluating long-term MACE post-CABG, in the present chapter I will validate the use of the SMART2 score in US Veterans that received CABG.

5.2 Published Manuscript

Citation

Validating the SMART2 Score in a Racially Diverse High Risk Nationwide Cohort of Patients Receiving Coronary Artery Bypass Grafting
Deo SV, Althouse A, Al-Kindi S, McAllister DA, Orkaby A, Elgudin YE, Fremes S, Chu D, Visseren FLJ, **Pell JP**, Sattar N.J Am Heart Assoc. 2023 Nov 7;12(21):e030757. doi: 10.1161/JAHA.123.030757. Epub 2023 Oct 27.PMID: 37889195

Manuscript

ABSTRACT

Introduction: We tested the potential of the Secondary Manifestations of ARTerial disease (SMART2) risk score for use in coronary artery bypass grafting (CABG) patients.

Methods and Results: We conducted an external validation of the SMART2 score in a racially diverse high-risk national cohort (2010 – 2019) that underwent isolated CABG. We calculated the pre-operative SMART2 score and modelled 5-year MACE (cardiovascular mortality + myocardial infarction + stroke) incidence. We evaluated SMART2 score discrimination at 5 years using c-statistic and calibration with O/E ratio and calibration plots. We analysed the potential clinical benefit using decision curves. We repeated these analyses in clinical

subgroups - diabetes mellitus (DM), chronic kidney disease (CKD) and poly-vascular disease, and separately in White and Black patients.

In 27,443, (mean age 65 years, 10% blacks) US Veterans undergoing CABG (2010 – 2019) nationwide, 5-year MACE was 25% and 27% were in high predicted risk (> 30% 5-year MACE). SMART2 score discrimination (c-statistic: 64) was comparable to the original study (c-statistic: 67) and was best in CKD patients (c-statistic: 66). However, it underpredicted MACE rates in the whole cohort (O/E ratio 1.45) as well in all studied subgroups. The SMART2 score performed better in White than Black patients. On decision curve analysis, the SMART2 score provides a net benefit over a wide range of risk thresholds.

Conclusions: The SMART2 model performs well in a racially diverse CABG cohort, with better predictive capabilities at the upper range of baseline risk and can therefore be used to guide secondary preventive pharmacotherapy.

Keywords: atherosclerotic vascular disease, coronary artery disease, coronary artery bypass grafting, myocardial infarction, risk prediction, external validation

CLINICAL PERSPECTIVE

1. What is new?

Risk prediction models to evaluate long-term major adverse cardiovascular events (MACE) after coronary artery bypass grafting (CABG) are very limited.

The SMART2 score can potentially fill this gap; we therefore used a nationally representative cohort of CABG patients to evaluate the predictive capability of the SMART2 score.

We report that in a racially diverse group of CABG patients, along with a reasonable predictive accuracy for CABG, the SMART2 score also demonstrates potential clinical usefulness.

2. What are the clinical implications?

We propose that clinicians use the SMART2 to risk stratify patients post-CABG and titrate the intensity of their secondary preventive therapies.

INTRODUCTION

Coronary artery bypass grafting (CABG) is among the most common adult cardiac surgical procedures worldwide. Although the prevalence of multi-morbidity in patients receiving CABG is increasing (Dinh et al., 2008), the 30-day mortality after CABG is low, approximately 1-2% (Jacobs et al., 2018). Yet, even after CABG, patients continue to suffer from major adverse cardiovascular events (MACE). Long term protection from these events depends upon the use of guideline directed medical therapy (GDMT) (Wolfe et al., 2021). Among various GDMT measures, aggressive lipid lowering therapy (LLT) is very important in reducing the progression of graft atherosclerosis and reducing low-density lipoprotein C concentrations improves saphenous vein graft patency.(Kulik et al., 2011). Recently, both the AHA and ESC defined a 'very high risk' (VHR) patient cohort, where they recommended lipoprotein C (LDL-C) target concentrations below 70 and 55 mg/dl respectively.(Grundy et al., 2019) Recent anti diabetes agents like glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium/glucose co-transporter 2 inhibitors (SGLT2i) have also been found to reduce MACE rates among patients with ASCVD(Deo et al., 2022b). However, a large study of CABG patients reported that only a fraction of eligible patients receive either therapy (Deo et al., 2022c). The financial burden, at the patient and more widely at the health system level often limits widespread use of these newer costly agents(Myers et al., 2019). In such circumstances, risk prediction models may help to identify those high-risk patients that would potentially benefit most from high-cost therapies. With this aim, Hageman and investigators recently introduced the Secondary Manifestations of ARTerial disease (SMART2) risk score.(Hageman et al., 2022b) This multivariable risk model predicts the risk for major adverse cardiovascular events (MACE) in patients with pre-existing atherosclerotic cardiovascular disease (ASCVD). This tool has been externally

validated in multiple cohorts and can be used to guide secondary preventive pharmacotherapy.(McKay et al., 2022) However, it has not yet been validated in CABG patients which is traditionally considered a high-risk cohort of patients with multivessel coronary artery disease and poly-vascular atherosclerosis. Current popular risk models for CABG patients were primarily developed to predict either peri-operative outcomes [Society of Thoracic Surgeons (STS) risk score, European system for cardiac operative risk evaluation (EuroSCORE)] or long-term mortality.(Lancaster et al., 2018, Urbanowicz et al., 2021) However understanding the risk for recurrent MACE is equally important as it can significantly affect the quality of life. The SMART2 score can accomplish that, but till date, has not been tested in patients after CABG.

We therefore applied the SMART2 score to a large US national cohort of CABG patients to evaluate its predictive capabilities and clinical usefulness. As patients at higher risk would be expected to derive the greatest absolute risk reduction from aggressive pharmacotherapy, we further tested the score in three clinically important subgroups: those with pre-existing diabetes mellitus (DM), chronic kidney disease (CKD; defined as an estimated glomerular filtration rate < 60 ml/min/m^2) or poly-vascular disease (defined as peripheral arterial or cerebrovascular disease plus coronary artery disease). The SMART2 model itself was developed in a predominantly White patient cohort. Hence, we also tested this score separately in White and Black patients.

METHODS

Overview of Data: The Veteran Health Administration (VA), with over 171 medical centres, is the largest integrated health care system in the United States (Fihn et al., 2014). Our primary data source for this study was the VA Surgical Initiative Project (VASQIP) which is maintained by the National Surgery Office.(Development) We identified consecutive patients that underwent CABG *(CPT codes: 33510:33516, 33533:33536,33517:33523*) and excluded those that received concomitant procedures, such as, valve repair/replacement, surgery for atrial fibrillation, ascending aorta replacement or extra-corporeal

mechanical support (Figure 5-1). We further sub-selected patients that had a baseline lipid profile measured within 4 months prior to surgery. The demographic, clinical, laboratory and pharmacy data for patients were obtained from VASQIP, which contains patient information closest to the surgery date. Each patient's race (self-reported at the time of hospital visit) was also abstracted from the VASQIP. If the necessary information was unavailable in the VASQIP database, we obtained it from their prior outpatient/inpatient visits or insurance claims records using relevant International Classification of Diseases (ICD) 9th / 10th edition or Common Procedure Terminology (CPT) codes. The study was approved by the R&D committee, North-east Ohio VA Healthcare system (#CY19-045) and individual patient consent was waived.

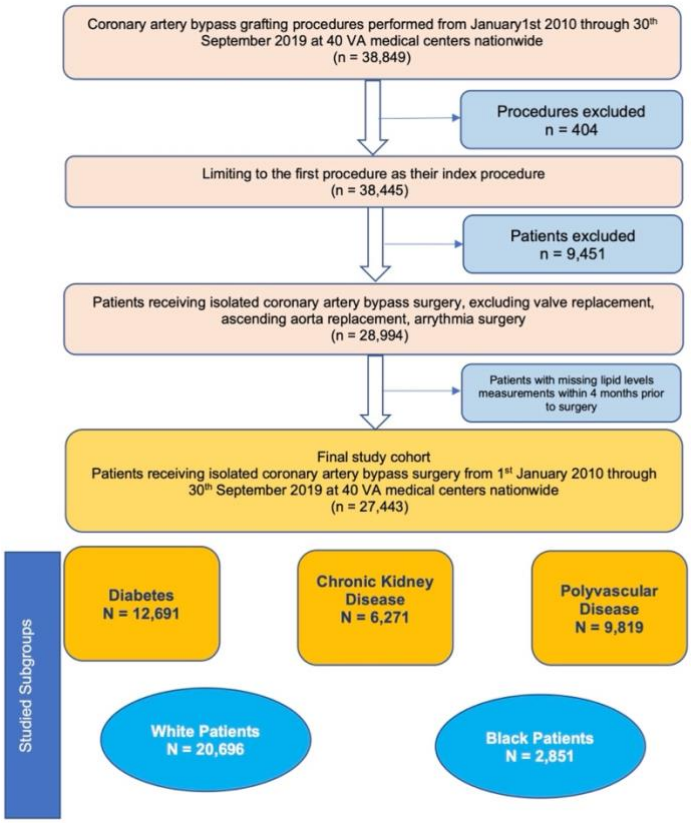


Figure 5-1. Flowchart of the cohort selection process in our study

Calculation of the Pre-operative SMART2 Score: The variables used to calculate the SMART2 score are age, sex, current smoking status, systolic blood pressure, diabetes mellitus, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral arterial disease, years since the diagnosis of vascular disease, high density lipoprotein (HDL) cholesterol, total cholesterol, estimated glomerular filtration rate (eGFR) and high sensitivity C-reactive protein (hs-CRP) (Table 5-1). The SMART2 score also contains a coefficient for geographical location, which in our cohort was North America. We observed missing information for HDL cholesterol (13%), total cholesterol (12%), eGFR (0.1%) and smoking status (0.01%). We used simple mean/mode imputation to fill the missing fields for these variables. As hs-CRP (which is not routinely tested prior to CABG) was largely missing from our data, we imputed hs-CRP values using Monte Carlo simulation as recommended by the SMART2 investigators.(Hageman et al., 2022b) We used the coefficients and equation from the supplemental section of the SMART2 manuscript to calculate the pre-operative SMART2 score for each patient. Further details on calculating the predicted MACE risk according to the SMART2 score is provided in the supplementary appendix.

Endpoint: We obtained vital status data (current till 31st December 2021 at the time of analysis) from the National Death Index, supplemented by information from the Social Security Index, Beneficiary Identification Records Locator Subsystem (BIRLS) and the Centre for Medicare and Medicaid Services (CMS).(Deo et al., 2022d, Deo et al., 2021) We further obtained the cause of death from the VA Mortality Data Repository (MDR)(Veterans Health Administration) and identified those patients that experienced cardiovascular mortality using the ICD 9th and 10th version codes listed as the primary cause of death. We identified the first date after surgery that patients were admitted for a primary diagnosis of myocardial infarction (MI) or ischemic stroke. We defined MACE as a composite of cardiovascular mortality, non-fatal MI, or non-fatal ischemic stroke and censored outcomes at 5 years after the date of surgery or the date of last follow-up, whichever occurred first.

Statistical Analysis: We report baseline characteristics of our cohort as median (interquartile range) or count (percentage) for continuous data and categorial data respectively. We stratified patients according to their predicted 5-year MACE risk as follows: low - less than 10%, moderate - 10% to less than 20%, high - 20% to less than 30%, & very high - 30% and beyond. We then compared the observed 5-year MACE incidence and predicted 5-year MACE risk for each risk group which was calculated using the Kaplan Meier method.

We tested discrimination using Harrell's C-statistic measured at the 5-year time point. We tested calibration-in-the-large (weak calibration) by calculating the observed/expected ratio (O/E ratio) and evaluated moderate calibration by plotting the predicted/expected vs observed with its 95% confidence interval over the whole range of predicted 5-year MACE estimates. To evaluate potential clinical effectiveness, we used two methods. Firstly, we tested whether the SMART2 score provides any incremental benefit over the VA projected risk of mortality (VA-PROM) score. The VA-PROM score is very similar to the STS score and developed by the VASQIP to predict 30-day mortality after CABG. Like the STS score, VA medical centres use the VA-PROM score to assess programmatic quality. The supplementary appendix contains further details regarding variables included in the VA-PROM score and its calculation. Using the net reclassification index model, we tested whether the SMART2 score was able to better reclassify patients into their correct risk categories against the 5-year MACE risk estimates obtained from a Cox proportional hazards model using the VA-PROM score. Secondly, we used the decision curve analysis tool introduced by Vickers et al.(Vickers and Elkin, 2006) In the decision curve analysis, the 5-year predicted MACE risk (SMART2 score) is fitted and plotted against two counter-factual scenarios, namely, *'treating none'* and *'treating all (current standard care)'* across a wide range of baseline risk estimates. We repeated all the above analyses in the three studied subgroups, namely DM, CKD (defined as an eGFR <60 ml/min/m^2) and poly-vascular disease (defined as having cerebrovascular or peripheral arterial disease prior to CABG) and separately in White and Black patients.

We conducted and reported results using the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) criteria for model validation (checklist present in the Supplementary Appendix).(Collins et al., 2015)

We used R.4.2.1 for statistical analyses; we used the 'riskRegression'(Gerds and Kattan, 2021) for model validation and calibration and the 'nricens'(Inoue, 2018) package for net reclassification.

Sensitivity Analyses: We performed sensitivity analyses to confirm our primary observations. Firstly, as we used imputation methods to fill missing fields, we calculated the c-statistic for the SMART2 score after limiting the cohort to patients with non-missing data (complete case analysis). Secondly, to confirm the temporal validity of the model, we calculated the c-statistic for the SMART2 score to predict 1-year, 3-year and 5-year MACE events. Figure S2 shows a diagrammatic representation of our analytic strategy.

Data Availability Statement: Due the sensitive nature of the data collected for this study the corresponding author cannot make the data available on request. Researchers qualified and credentialled to conduct research at the VA can request access to the data using the regular pathway. The authors have made code available for download at: https://github.com/svd09/smart2_validate.

RESULTS

Baseline Patient Characteristics: Nationwide, in 42 VA medical centres during 2010-2019, 27,443 patients [median age 66 (IQR: 61, 70) years, female 1.1%, 75% White patients, 10% Black patients] underwent isolated CABG. The prevalence of diabetes mellitus, chronic kidney disease and poly-vascular disease was 12,691 (46.2%), 6,271 (22.8%) and 9,819 (35.7%) respectively (Table 5-2). Over the 5-year study period, the cumulative incidence for MACE in the whole cohort was 25.7% (95%CI: 25.1, 25.3). Among studied clinical subgroups, it was highest for CKD patients at 37.9% (95%CI: 36.6, 39.2), followed by those with poly-vascular

disease [33.4% (95%CI: 32.4, 34.4)] and DM [30.3% (95%CI: 29.4, 31.2)]. Compared to White patients, Black patients had a substantially higher 5-year MACE rate [29.1 (27.2, 31) % vs 25.7 (25.1, 26.4) %].

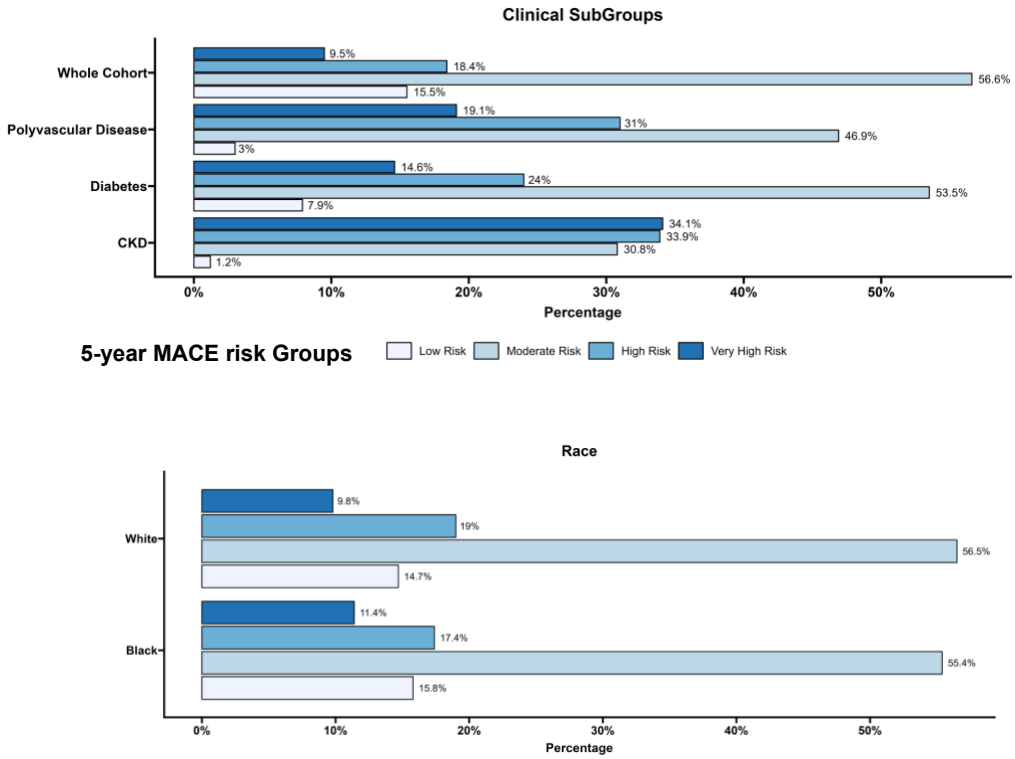


Figure 5-2. 5-year MACE risk according to clinical and race groups

The median predicted 5-year MACE risk (SMART2 score) for the whole cohort was 15 (IQR: 11.4, 20.9) %, with 18% and 9% belonging to the high and very-high risk groups. CKD patients had the highest median 5-year predicted MACE risk [24.7 (18.2, 33.9) %], then poly-vascular disease [201. (15.3, 27.1)] and lastly DM [17.3 (13.2, 24.3)]. However, both Black [15.1 (11.3, 21.5)] and White [15.2 (11.5, 21.7)] patients had very similar 5-year predicted risks (Figure 5-2).

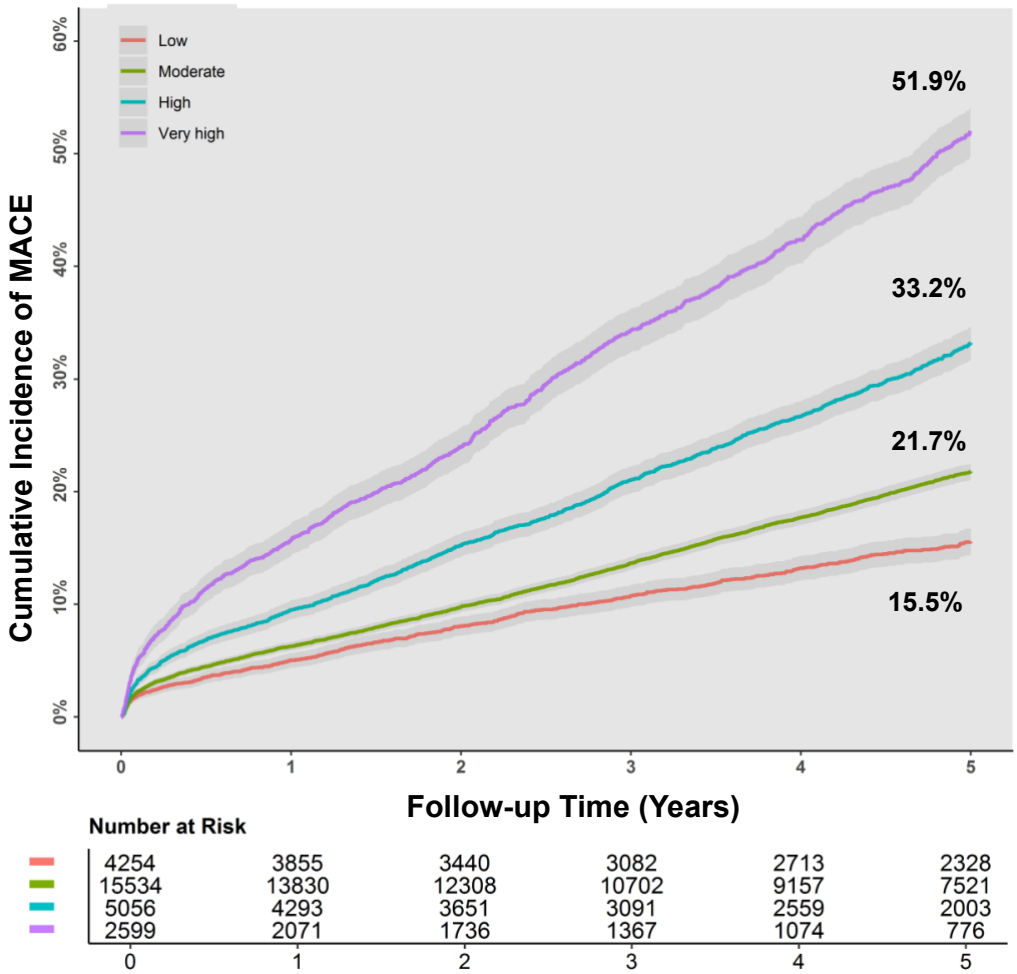
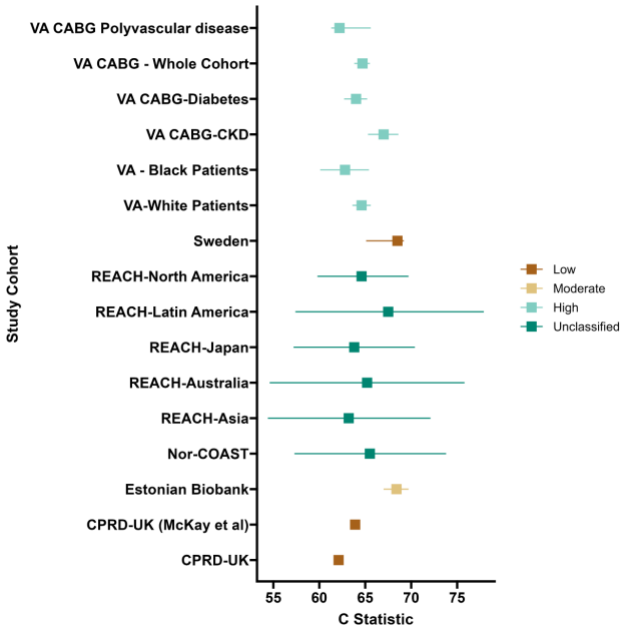


Figure 5-3. 5-year Cumulative observed MACE incidence for each SMART2 risk group.

estimates. Among clinical subgroup, CKD patients had the highest predicted 5-year MACE risk with 67% in the high or very high-risk categories. Black and White patients had similar number of patients in the high or very high-risk category (28.8 % 28.8%) (Figure 5-2).

The observed 5-year MACE rate increased incrementally over each predicted risk group but were higher than the predicted 5-year MACE estimates (Figure 5-3). For the whole cohort, the 5-year observed MACE rates in the low (< 10%), moderate (10 - < 20%), high (20 - < 30%) and very high-risk groups (> 30%) were 15.5%, 21.7%,33.2% and 51.9% respectively (Table 5-3). This incremental

increase for each predicted risk group was observed across all studied clinical subgroups as well as in White and Black patients (Table 5-3).



Cohort	Risk category	Harrell's C-Statistic
CPRD-UK	Low	62.1 (61.8, 62.3)
Sweden	Low	68.5 (65.1, 69.2)
CPRD-UK (McKay et al)	Low	63.9 (63.6, 64.2)
Estonian Biobank	Moderate	68.4 (67, 69.7)
VA CABG	High	64.7 (63.8, 65.5)
VA CABG-DM	High	63.6 (62.7, 65.2)
VA CABG-CKD	High	66.2 (64.6, 68.6)
VA CABG Polyvascular disease	High	62.2 (61.3, 65.6)
REACH-North America	Unclassified	64.6 (59.8, 69.7)
REACH-Asia	Unclassified	63.2 (54.5, 71.2)
REACH-Japan	Unclassified	63.8 (57.2, 70.4)
REACH-Latin America	Unclassified	67.5 (57.4, 77.9)
REACH-Australia	Unclassified	65.2 (54.6, 75.8)
Nor-COAST	Unclassified	65.5 (57.3, 73.8)
VA-White Patients	High	64.6 (63.6, 65.6)
VA-Black Patients	High	62.8 (60.1, 65.4)

Figure 5-4. Harrell's c-statistic reported in various cohorts

The Harrell' s c-statistic for the SMART2 score in the whole cohort was 64.7 (63.8, 65.5) and was highest in the CKD subgroup [c-statistic 67 (65.3, 68.6)]. The overall and sub-group c-statistic values observed in our data were very similar to those reported by the SMART2 investigators and a prior validation study by McKay et al(McKay et al., 2022) The c-statistic for the SMART2 score was lower in black patients than white patients (Figure 5-4). On calibration-in-the-large, the SMART2 score predicted 5-year MACE risk underestimated the observed MACE risk, in the whole cohort [O/E ratio 1.45 (95% CI: 1.42, 1.49)] and for the whole cohort and for each studied subgroup (Figure 5-4). Among clinical subgroups, the c-statistic was highest and O/E ratio lowest for the CKD patients (Figure 5-5). The SMART2 score was better at predicting 5-year MACE risk for White patients compared to Black patients, as evidenced by the lower c-statistic and higher O/E ratio among Black patients (Figure 5-6). These primary results were supported when c-statistic were calculated using complete case-analysis (Table 5-4). Interestingly, the c-statistic for the SMART2 score (overall and in

each studied subgroup) improved over time (1-year MACE: c-statistic: 61, 3-year MACE, c-statistic: 62.7, 5-year MACE: c-statistic: 64.7) (Table 5-5).

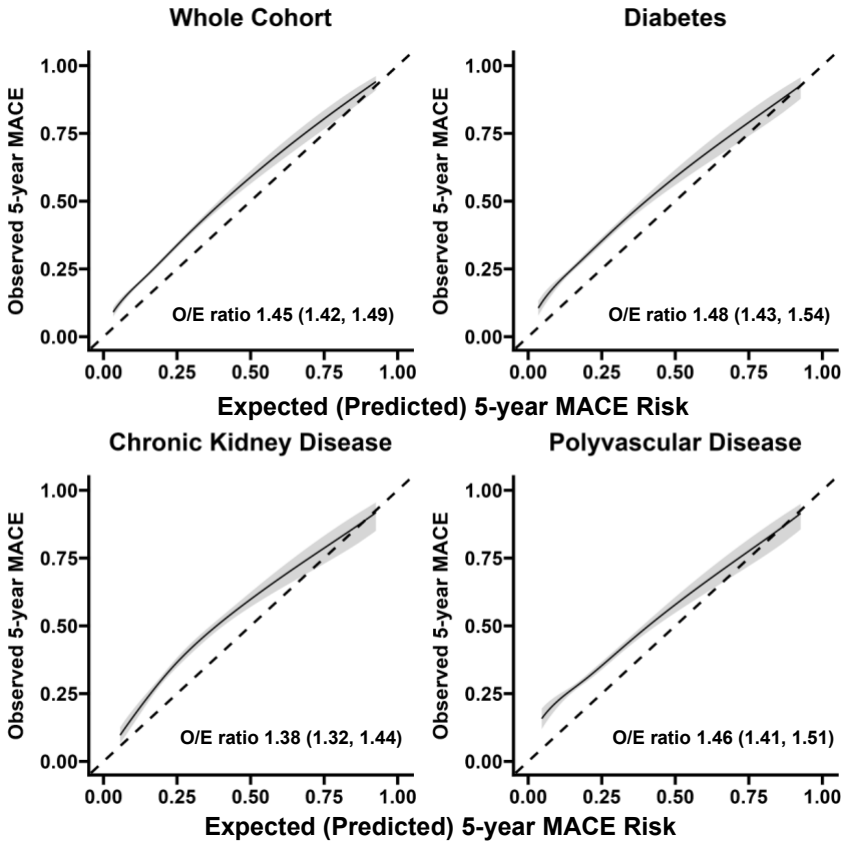


Figure 5-5. Calibration plot, overall and in each clinical group

Compared to the risk prediction obtained using the VA-PROM, the SMART2 score improved risk group classification for the study cohort and in each clinical subgroup. This improvement was most marked for the CKD and Black patients while the benefit was minimal in patients with poly-vascular disease (Table 5-6). Using decision curve analysis, we observed that the SMART2 score was better than routine care in predicting 5-year MACE events in patients at high and very high risk (20 – 50 %). Among CKD patients, this benefit even extended to those at extremely high risk (SMART2 score 5-year MACE prediction risk $\leq$ 70%) (Figure 5-7). Clinical potential net benefit was also observed in both White and Black patients.

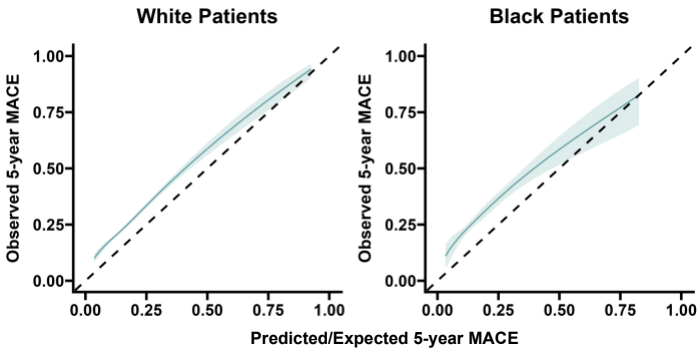


Figure 5-6. Calibration plots according to race groups

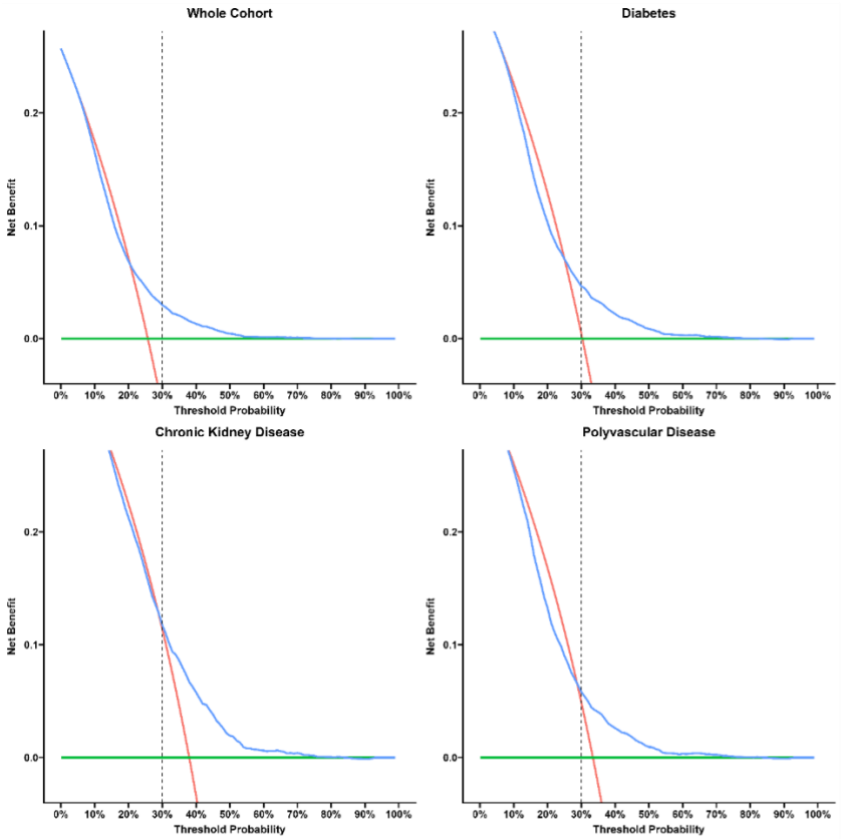


Figure 5-7. Decision curves plotted, overall and for each clinical group

We externally validated the SMART2 prediction model in a nationally representative cohort of high-risk CABG patients over a five-year time-period. We report that the overall predictive capability of the SMART2 score in our CABG cohort was comparable to that observed by the SMART2 investigators who used data from multiple European registries. We also observed that the SMART2 score performed better in the CKD subgroup, i.e., in those at the upper range of 5-year MACE risks.

Patients undergoing CABG often have long-standing, multi-vessel complex coronary artery disease, a high atherosclerotic burden and associated long-term comorbidities. Therefore, even after surgical revascularization, these patients may suffer from recurrent MACE events. Understanding the baseline risk is key to initiating appropriate individualized pharmacotherapy. However, most widely used risk models for CABG patients evaluate peri-operative and long-term mortality(Lancaster et al., 2018, Urbanowicz et al., 2021, Wu et al., 2012). Multiple recent studies reported that, in spite of being at high risk for MACE, CABG patients often received suboptimal pharmacotherapy after surgery (Deo et al., 2022a, Deo et al., 2022c) (Zheutlin et al., 2022). Therefore, increasing the adoption of risk models like the SMART2 score may help to stratify patients into groups according to their baseline risk. This may allow clinicians to reserve the more costly agents for those high-risk individuals that require further risk reduction. Such an individualized approach may benefit both patients' and the healthcare system. Among currently available risk models for patients with established ASCVD, we believe that the updated SMART2 score is ideal for use in this context. It has already been validated in geographically diverse cohorts with varying risk profiles, and we now demonstrate that it can also be used with similar accuracy in CABG patients (Hageman et al., 2022b). Our net reclassification models demonstrated that the SMART2 score improves risk stratification across racial and clinical subgroups and the decision curve analysis further reported a net benefit in patients that had baseline SMART2 scores between 10 and 50%. Hence, the score can effectively triage and identify patients at moderate and high risk for 5-year MACE. An online calculator and application for use on personal devices is also provided by the SMART2

investigators (U-prevent). This additional tool makes score calculations easy to use and implement at the bedside.

Readers should interpret our study results on the background of certain limitations. As we used a cohort of US Veterans, we were not able to evaluate the SMART2 score separately for men and women. Although a recent study using primary care data reported comparable validation metrics in both sexes, this may not translate to CABG patients as, compared to men, women are reported to suffer from higher MACE rates after CABG. (Gaudino et al., 2021) (McKay et al., 2022) However, that would make using such a risk stratification tool even more important in women. Our study reported important differences in the performance of the SMART2 score among White and Black patients. Although our cohort is racially diverse, we feel future work should focus on testing the validity of our observations in larger more racially/ethnically diverse cohorts. We defined MACE events using ICD codes which are susceptible to administrative coding errors. However, our study is likely the first to evaluate the SMART2 score in a large 'high-risk' nationally representative cohort of CABG patients with further analyses in clinically important subgroups. Our study, therefore, demonstrated that wider use of the SMART2 score may be a useful tool in guiding effective pharmacotherapy after CABG.

CONCLUSION

The SMART2 prediction model performed well in a racially diverse group of high-risk CABG patients, with better predictive capabilities at the upper range of baseline risk. These results suggest SMART2 could be helpful in patients post CABG to define future risks and intensity of secondary preventative efforts.

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5.3 Appendix

Table 5-1. Variables included in the SMART2 score

This table presents the variables included in the regression equation for the SMART2 risk prediction score. We also present how these variables were obtained in our cohort. The score obtained is the patients predicted risk for MACE at that time point. Along with these variables, the SMART2 score also considers the country from which the cohort is developed, and the time point for which the risk is to be predicted. CAD – coronary artery disease, eGFR – estimated glomerular filtration rate, HDL – high density lipoprotein cholesterol, hs-CRP – high sensitivity C-reactive protein

Variable used in SMART2 score	Definition of variable used in external validation using our cohort
Age in years	Age in years at date of surgery
Male	male
Current smoker	Obtained from VASQIP data (already coded)
Systolic blood pressure	Systolic blood pressure obtained at visit prior to CABG.
Diabetes mellitus	Diabetes mellitus
History of CAD	All have history of CAD
History of cerebrovascular disease	Obtained from the VASQIP data (already coded)
Abdominal aortic aneurysm	Obtained using ICD9/ICD10 codes from VASIP data entered at CABG admission
Peripheral artery disease	Obtained from VASQIP data (already coded)
Years since first diagnosis of vascular disease (within 1 year, 1 – 5 years, > 5 years)	Obtained from outpatient visit data using ICD9/ICD10 codes for CAD, PAD, CeVD
HDL-cholesterol in mmol/L	Obtained from laboratory data, most recent level prior to CABG selected
Total cholesterol in mmol/L	Obtained from laboratory data, most recent level prior to CABG selected
eGFR in mL/min/1.73m^2	Calculated from serum creatinine, BMI, sex and race entered into VASQIP at the time of CABG admission
hs-CRP in mg/dL	Simulated values obtained using mean and standard deviation reported in the SMART Score paper.

Table 5-2. Descriptive characteristics of the study cohort.

Baseline characteristics observed in our cohort of 27,443 patients undergoing coronary artery bypass grafting at 40 different VA medical centres (2010 – 2019). Hba1c – Glycosylated Hemoglobin a1, SD – standard deviation

Characteristics	Mean (SD) / Count (Percentage)
Cohort demographics	
Age (years)	65.69 (7.61)
Females	314 (1.1)
Race	
White	20696 (75.4)
Black	2851 (10.4)
Others	3896 (14.2)
Comorbidities	
Diabetes mellitus	12691 (46.2)
Chronic kidney disease	6271 (22.9)
Polyvascular disease	9,819 (35.8)
Heart failure	807 (2.9)
Obese	12711 (46.3)
Peripheral arterial disease	5213 (19)
Dyslipidemia	10422 (38)
Current Smoker	6773 (24.7)
Recent acute coronary syndrome	3645 (13.3)
Atrial fibrillation	3113 (11.3)
Prior myocardial infarction	2836 (10.3)
Left ventricular ejection fraction	49.01 (13.89)
Laboratory parameters	
Hemoglobin (gm/dl)	13.48 (1.87)
HbA1c (%)	6.80 (4.25)
Low density lipoprotein-C (mg/dl)	93.66 (37.26)
High density lipoprotein (mg/dl)	39.82 (11.21)
Total Cholesterol (mg/dl)	163.95 (41.76)

Table 5-3. 5-year MACE incidence in clinical and race subgroups

This table presents the observed cumulative 5-year MACE incidence for patients classified according to their predicted SMART2 risk groups. MACE – major adverse cardiovascular event, SMART2 – the Secondary Manifestations of ARTerial disease

	5-year Predicted MACE risk category as per the SMART2 score			
	Low Risk (< 10%)	Moderate Risk (10 - <20%)	High Risk (20 - <30%)	Very High Risk (≥ 30%)
Whole Cohort	15.5%	21.7%	33.2%	51.9%
Clinical Categories				
Diabetes	18.3%	24.2%	34.6%	52.4%
Chronic Kidney Disease	19.3%	23.2%	35.5%	54.1%
Polyvascular Disease	25%	25.9%	34.9%	51.4%
Race Categories				
White	15.4%	21.1%	32.9%	51.2%
black	21.4%	24.1%	36.6%	53.7%

Table 5-4. Results of complete case analysis

This table presents the c-statistic for 5-year MACE using the complete case-analysis method. We observed that the SMART2 score discrimination for both methods were quite comparable. CABG – coronary artery bypass grafting, CKD – chronic kidney disease, DM – diabetes mellitus, VA – Department of Veterans Affairs

Cohort (sample size)	Complete case analysis (only patients with complete data)	Primary analysis (mean/mode imputation used to fill missing information)
VA CABG (n = 22873)	64.2	64.7
VA CABG-CKD (n = 5157)	66.5	66.2
VA CABG-DM (n = 10507)	63.7	63.6
VA CABG Polyvascular Disease (n = 8115)	62.3	62.2
VA- White patients (n = 17264)	64	64.6
VA- Black patients (n = 2306)	62.1	62.8

Table 5-5. Time dependent Harrell's c-statistic

This table presents the c-statistic for the SMART2 score at 1, 3 and 5-years. We observed that the discrimination of the model improved over time. CABG – coronary artery bypass grafting, CKD – chronic kidney disease, DM – diabetes mellitus, VA – Department of Veterans Affairs

Cohort (sample size)	c-statistic (5-year MACE)	c-statistic (3-year MACE)	c-statistic (1-year MACE)
VA CABG	64.7	62.7	61.0
VA CABG-CKD	66.2	64.7	62.1
VA CABG-DM	63.6	62.7	61.1
VA CABG Polyvascular Disease	62.2	60.9	59.2
VA- White patients	64.6	62.3	60.2
VA- Black patients	62.8	62.7	62.8

Table 5-6. Net reclassification index

This table presents the net reclassification index for the SMART2 score against a Cox proportional hazards model using the VA-PROM score as the predictor. We observed that the SMART2 score improved risk group classification for the whole cohort. This was numerically highest in the CKD subgroup and for black patients. CKD – chronic kidney disease, SMART2 – the Secondary Manifestation of ARTerial disease 2, VA-PROM – VA-projected risk of mortality

Studied Group	Net Reclassification Index	Bootstrapped confidence interval
Whole Cohort	0.07	0.06, 0.09
Clinical Categories		
Diabetes	0.03	0.01, 0.06
Chronic Kidney Disease (CKD)	0.09	0.05, 0.12
Poly-vascular Disease	0.01	-0.01, 0.04
Race Categories		
White	0.07	0.04, 0.09
Black	0.10	0.05, 0.15

5.4 Author Declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	Validation the SMART2 Score in a Racially Diverse High-Risk Nationwide Cohort of Patients Receiving Coronary Artery Bypass Grating Deo SV, Althouse A, Al-Kindi S, McAllister DA, Orkaby A, Elgudin YE, Fremes S, Chu D, Visseren FLJ, Pell JP, Sattar N.J Am Heart Assoc. 2023 Nov 7;12(21): e030757. doi: 10.1161/JAHA.123.030757. Epub 2023 Oct 27. PMID: 37889195 SVD, YE – Louis Stokes Cleveland VA Medical Center, Cleveland, USA AA, DC – Universityf of Pittsburgh, PA, USA SAK – Houston Methodist Hospital, TX, USA AO – Harvard University, MA, USA SF – University of Toronto, ON, Canada FLJV – Utrecht University, Utrecht, Netherlands NS, JP, DAM, SVD – University of Glasgow, Glasgow, UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	SVD, JP, NS, DAM, SAK
Data Curation	SVD
Formal Analysis	SVD
Investigation	SVD
Methodology	SVD, AA, JP, NS, DAM
Project Administration	JP, NS
Visualisation	SVD
Writing – original draft	SVD
Writing – review & editing	JP, NS, YE, DC, AO, SF, FLJV

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 6: Paper 5

6 The impact of residential social deprivation on prediction of heart failure in patients with type 2 diabetes mellitus: External validation and recalibration of the WATCH-DM score using real world data.

6.1 Preface

Clinical risk prediction models are utilized to inform healthcare delivery and guide shared decision-making between healthcare provider and patient. Heart failure is rapidly emerging as a global epidemic in the past decades (Dunlay and Roger, 2014). Additionally, recent evidence has reported that type 2 diabetes doubles the risk of incident heart failure (Kenny and Abel, 2019). However, apart from clinical factors, I recently investigated and reported that the social determinants of health (SDoH) may also impact heart failure hospitalization among people with type 2 diabetes (Deo et al., 2023a). In fact, the American Heart Association considers SDoH to be a very important factor in determining cardiovascular health; hence, they have introduced it as a covariate in the recently introduced Predicting Risk of CVD EVENTs (PREVENT) equation (Khan et al., 2024). However, a systematic review of model predicting the risk of heart failure in type 2 diabetes reported that among 15 published models, only one model (UK based QDIABETES score) included the SDoH as a covariate in the risk calculations (Razaghizad et al., 2022). Among the scores reviewed in this study, the WATCH-DM score has been externally validated using cohort data but has not been tested using large real-world data. Hence, I validated the WATCH-DM score in a large real-world cohort of US Veterans with type 2 diabetes. I further evaluated whether residential SDoH changed and the predictive accuracy and modified the original score to include the residential SDoH as a covariate in the model. The new score sdiWATCH-DM was packaged as free calculator for easy use.

6.2 Published Manuscript

Citation

Impact of Residential Social Deprivation on Prediction of Heart Failure in Patients with Type 2 Diabetes: External Validation and Recalibration of the WATCH-DM Score Using Real World Data. Deo SV, Al-Kindi S, Motairek I, McAllister D, Shah ASV, Elgudin YE, Gorodeski EZ, Virani S, Petrie MC, Rajagopalan S, Sattar N. Circ Cardiovasc Qual Outcomes. 2024 Mar;17(3):e010166. doi: 10.1161/CIRCOUTCOMES.123.010166. Epub 2024 Feb 8.

PMID: 38328913

Manuscript

WHAT IS KNOWN: Heart failure risk prediction models like WATCH-DM exist for patients with type 2 diabetes, but few are validated in real-world diverse cohorts. Social deprivation impacts cardiovascular disease risk, but few models account for socioeconomic factors.

WHAT THE STUDY ADDS: This study validated WATCH-DM in a large US cohort, finding it underestimates heart failure risk in socially deprived patients. The WATCH-DM score was recalibrated using a social deprivation index, improving model accuracy. An online tool was created for clinicians to estimate heart failure risk using the recalibrated WATCH-DM score.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) (Joseph et al., 2022). Regardless of baseline ventricular systolic function, patients with T2DM have 2-3-fold increased risk for CVD, especially heart failure (both preserved and reduced ejection fraction) (Joseph et al., 2022). The expanding armamentarium of cardio-reno-protective medications (e.g Glucagon like Peptide-1 receptor

agonist (GLP1RA),Sodium Glucose Co-transporter-2 receptor inhibitor (SGLT2i), and non-steroidal mineralo-corticosteroid receptor antagonist (MRA) in T2DM have recently transformed pharmacotherapy with clinical guidelines now recommending that these agents be initiated in T2DM patients at high-risk for CVD (Fox et al., 2015). While these medications also uniquely reduce the risk for incident heart failure hospitalization (HFH) (Davies et al., 2022), they unfortunately remain underutilized in clinical practice (Adhikari et al., 2022, Deo et al., 2022c, Mahtta et al., 2022).

In this regard, accurate heart failure risk prediction in patients with T2DM is important to allocate resources, focus targeted therapies, especially SGLT2i and GLP1RA, and help overcome the current inertia of prescribing cardioprotective therapies. Many risk models do currently exist for predicting risk of HF in patients with T2DM (Kanda et al., 2022, Razaghizad et al., 2022, Segar et al., 2019, Razaghizad et al., 2023). However, the majority of these models have been derived from studies that may not reflect real-world population (clinical trial data or prospective studies). For example, the WATCH-DM score and RECODe risk scores were developed using the ACCORD trial, while the TRS-HF_{DM} was created using the SAVOR-TIMI 53 study. In fact, a recent systematic review reports only one score, the QDIABETES, was created using real world data (primary care data from the UK) (Razaghizad et al., 2022). As prior literature has reported differences in patient characteristics between trial or prospectively developed cohorts and real-world data, there is a need to evaluate these models using routinely collected electronic health care data (Fry et al., 2017, Keyes and Westreich, 2019). Therefore, at present, it is unclear whether risk prediction calculated from these models can be generalized to diverse patients in real-world settings. Additionally, studies have already demonstrated that the social determinants of health (SDoH) are associated with an increased risk of cardiovascular disease and heart failure (Bevan et al., 2023, Bevan et al., 2020, Li et al., 2020). However, despite this evidence, current risk scores do not account for these SDoH and may represent a missed opportunity to improve patient care. Recent efforts are already underway to develop polysocial risk scores that incorporate a variety of socioeconomic factors along with clinical

data; these may improve risk prediction and enhance resource allocation. A prior study demonstrated mis-calibration of the American Heart Association/American College of Cardiology Pooled Cohort Equations Risk Model for ASCVD risk prediction in patients residing in socially deprived neighbourhoods (Bevan et al., 2023) .Recent studies also demonstrated increased heart failure hospitalization rates in patients with T2DM residing in deprived neighbourhoods (Li et al., 2020, Deo et al., 2023a). However, despite these observations, the UK-based QDIABETES score is the only heart failure hospitalization risk score that included measure of social deprivation (Hippisley-Cox and Coupland, 2015).

From the various recent scores developed for predicting heart failure in T2DM, the WATCH-DM score is externally validated in multiple cohorts (mostly trials, and one single-centre electronic health record dataset with a small number of heart failure events) (Segar et al., 2022). It uses readily available clinical data and provides a simple point scoring system. We, therefore, sought to externally validate the WATCH-DM score in a large contemporary US-based multi-centre real-world electronic health data. We further sought to test the hypothesis that residential SDoH may influence the scores predictive accuracy and, if needed, recalibrate the score using SDoH.

RESEARCH DESIGN AND METHODS

Data and resource availability: The data that support the findings of this study are only available to researchers credentialled to conduct research at the VA. Code used for statistical analyses are available at: *https://github.com/svd09/recalibrate_watchdm_sdi*. The study was approved by the Research and Development Committee of the Northeast Ohio VA Healthcare system and individual patient consent was waived.

Overview of the Cohort: The Department of Veterans Affairs (VA) healthcare system, with approximately 9 million beneficiaries, is the largest single healthcare provider in the US. The primary source of data for this study was the Corporate Data Warehouse, a central secure repository of information obtained

from the electronic health records of US Veterans receiving in-patient and out-patient care. Researchers can link clinical information with data regarding laboratory and other tests to create an accurate detailed health trajectory for each patient. Information regarding clinical encounters occurring outside the VA healthcare system is also provided in the Corporate Data Warehouse when this care has been paid by the VA. We initially identified US Veterans that received outpatient care with a diagnosis of diabetes mellitus in 2010 across all VA healthcare locations and defined their first visit during this year as they index visit. We excluded patients that had current or prior heart failure. We used a time-period of 1 year prior to the index visit to collect information regarding their clinical characteristics and laboratory results. We used this information to obtain the points for each covariate included in the WATCH-DM score and then obtained the total points for each patient. We observed missing information regarding body mass index (22.5%), creatinine (15%), HbA1c (1.2%), systolic blood pressure (1.6%), and diastolic blood pressure (1.6%). Age, prior myocardial infarction, and prior coronary artery bypass grafting did not have any missing data. We filled the missing fields using mean imputation, with the mean values obtained from the non-missing information for each variable. We identified the patients' residential ZIP code at the time of the index visit.

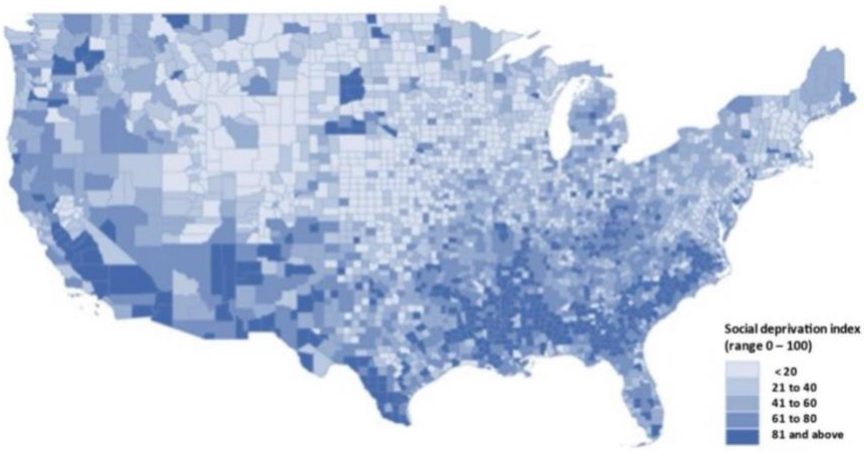


Figure 6-1. Social Deprivation Index quintile at the zip-code level in the US

Social deprivation index (SDI): The 2015 SDI is a composite metric of socioeconomic status derived at the ZIP code level. This index is derived using 7 domains from the American Community Survey identified through factor analysis: Income [Percent population less than 100% FPL (population under 0.99 /total population)], education [Percent population 25 years or more with less than 12 years of education (population with less than high school diploma or 12 years of education/total population], Employment [Percent Non-employed (not in labour force + unemployed) / (civilian + not in the labour force) for the population 16-64 years], Housing [Percent population living in renter-occupied housing units (Renter occupied housing units/ (Owner-occupied housing units + Renter occupied housing units), Percent population living in crowded housing units (Tenure by Occupants Per Room – a population with ≥ 1.01 occupants per room in Owner-occupied housing units and Renter occupied housing units) / total population], Household Characteristics [Percent single-parent households with dependents < 18 years (total single-parent households (male and female) with dependents <18 years)/total population)], Transportation [Percent population with no car (population with no vehicle available/total population)], and demographics [Percent high needs population, namely (population under 5 years of age + women between the ages of 15-44 years + everyone 65 years and over)/total population]. The final SDI measure is a weighted total of all these measures and ranges from 0 (least socially deprived) to 100 (most socially

deprived). For our study, using the residential ZIP code derived SDI we grouped patients as follows: group 1 (least deprived) SDI: < 20, group2: 21 - 40, group 3: 41 - 60, group 4: 61 - 80, and group 5 (most deprived) 81 – 100 (Figure 6-1). These cut-offs were used to represent fixed percentiles throughout the US ZIP codes (meaning that do not vary by cohort used) with each subsequent group representing a higher level of social deprivation as derived from the patients residential ZIP code.

The WATCH-DM score: The WATCH-DM score used in our study includes the following covariates: age, body mass index, systolic blood pressure, diastolic blood pressure, serum creatinine, high density lipoprotein cholesterol concentration, prior myocardial infarction, prior coronary artery bypass grafting and the HbA1c level. Users score patients on each covariate and obtain a point total (Table 6-1). They can then use a look-up table which converts the points into 5 groups from group I (very low risk) to group V (very high risk) with a corresponding 5-year risk estimate (Table 6-2).

In our study, we defined the incidence of heart failure as the first occurrence of heart failure hospitalization over the five-year follow-up period, i.e., being admitted with a primary diagnosis of heart failure ascertained by the International Classification of Diseases (ICD)9^{th} (428.xx) and 10^{th} (I50.x) version codes. In patients that had heart failure hospitalization, we further obtained the admission date for that event.

Statistical analysis:

We reported continuous and categorical data as mean (standard deviation (SD)) or count(percentage) respectively. For patients that died during follow-up, we obtained their date of death and calculated the duration from the index date and death date. For those alive, we censored their follow-up at 5 years, as all patients that were alive continued to receive care at VA medical centres beyond that time-period. We used the Kaplan Meier method to obtain the cumulative incidence for heart failure hospitalization. We first fit and then validated the

WATCH-DM score in the whole cohort. After calculating the WATCH-DM score for all 1,065,691 patients we divided them into five groups- from group I (very low risk) to group V (very high risk). We initially evaluated the discrimination metrics of the score. Discrimination is the ability of the risk model to separate patients into groups with incrementally increasing risks. To evaluate this, we calculated and then plotted the heart failure hospitalization incidence of each WATCH-DM risk group and graphically evaluated the extent of curve separation between groups. We fitted a cox proportional hazards model with the WATCH-DM group as the covariate and evaluated the relative risk for heart failure hospitalization in each group with group I as the reference. We then refitted this model including the SDI quintile as a second covariate. To examine the incremental benefit of adding the SDI to the original WATCH-DM score, we compared model fits using the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), an analysis of variance (ANOVA) test. We used cross-validation (100 bootstrapped samples) to perform internal validation. We calculated the Harrell's c-statistic and Brier score (lower value is better) to quantify the discrimination of the score. Risk score calibration is its ability to accurately predict the absolute risk at the studied timepoint, i.e., calibration measures the difference between the expected (predicted) and observed (actual) cohort risk. We initially split the data into deciles of the predicted risk. We created a calibration plot and numerically evaluated the calibration with the Greenwood Nam D'Agostino (GND) test (Demler et al., 2015). The GND test is a goodness-of-fit test like the Hosmer Lemeshow test for Cox models and can be applied for evaluating external calibration. Patients are grouped into *n* (normally deciles) of predicted risk, and the ratio of the observed and estimated events for each group is calculated to obtain a chi-square test value and the corresponding p-value with *n-1* degrees of freedom. The calibration plot is a graphical representation of the expected (x-axis) and observed (y-axis) estimates (Steyerberg and Vergouwe, 2014). The model calibration was visually assessed against a diagonal line, which is the 'perfect' calibration fit.

Using the same methods stated above, we then externally validated the risk score in each quintile of the SDI. Our preliminary observations demonstrated

wide variation in the incidence of heart failure hospitalization across quintiles of the SDI. We, therefore, further re-calibrated the WATCH-DM score according to the SDI quintile groups. We used the calibration-in-the-large method to obtain a correction factor which was then included in the prediction model to obtain the revised risk estimates (Hageman et al., 2022a). Briefly, the correction factor is a point estimate obtained from the observed and expected risk estimates in each quintile of the SDI. The supplement contains more details regarding correction factor calculation. The risk prediction obtained after re-calibration was then tested with the calibration plots and GND test. Finally, to evaluate the potential clinical usefulness of the re-calibrated model, we fit decision curves to evaluate its 'net benefit' (Vickers et al., 2019).

RESULTS

Our validation cohort included 1,065,691 patients (mean age 67.45 years, 3.33% female patients, 75.55% White patients, and 6.26% Hispanic patients) that received outpatient care during 2010 at VA medical centres nationwide. Patients in our cohort resided in 34,596/41,704 (82.9%) unique zip codes in the US. For patients included in our cohort, the ZIP code level median household income was $ 46,791 (IQR: $37,963, $58,689) and the median household value was $ 119,600 (IQR: $84,000, $181,500). The median single parent households, median unemployment and median poverty levels observed in our data were 14% (IQR: 9, 19), 7.9% (IQR: 5, 11.5) and 12.4% (7, 19.5) respectively. The prevalence of preexisting coronary artery disease, cerebrovascular disease, peripheral arterial disease was 31.02%, 11.14% and 14.97% respectively; 13.22% have chronic kidney disease (eGFR < 60 ml/min/m^2) and an additional 2.07% were dialysis dependent (Table 6-3).

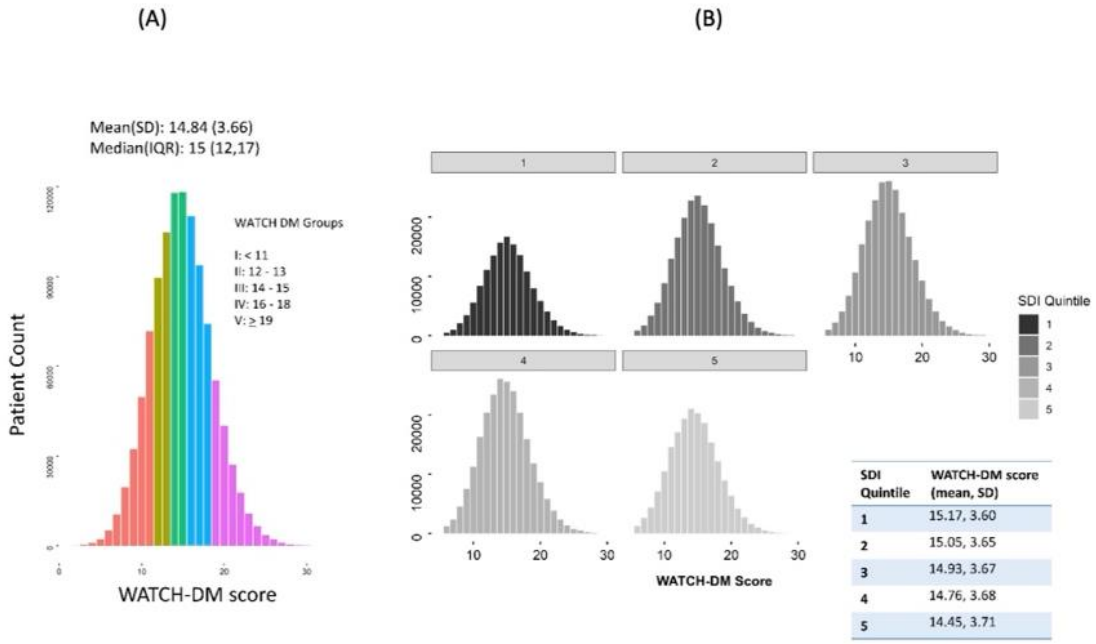


Figure 6-2. The WATCH-DM score in the cohort

The distribution of the WATCH-DM score observed (A) overall, and (B) according to the quintile of the SDI.

The mean (SD) WATCH-DM score in our cohort was 14.84 (3.66), the median score was 15 (Inter-quartile range: 12,17) and the maximum was 33 (Figure 6-2). From group I to group V of the WATCH-DM score we observed a gradual increase in the prevalence of all traditional cardiovascular risk factors (Table 6-3).

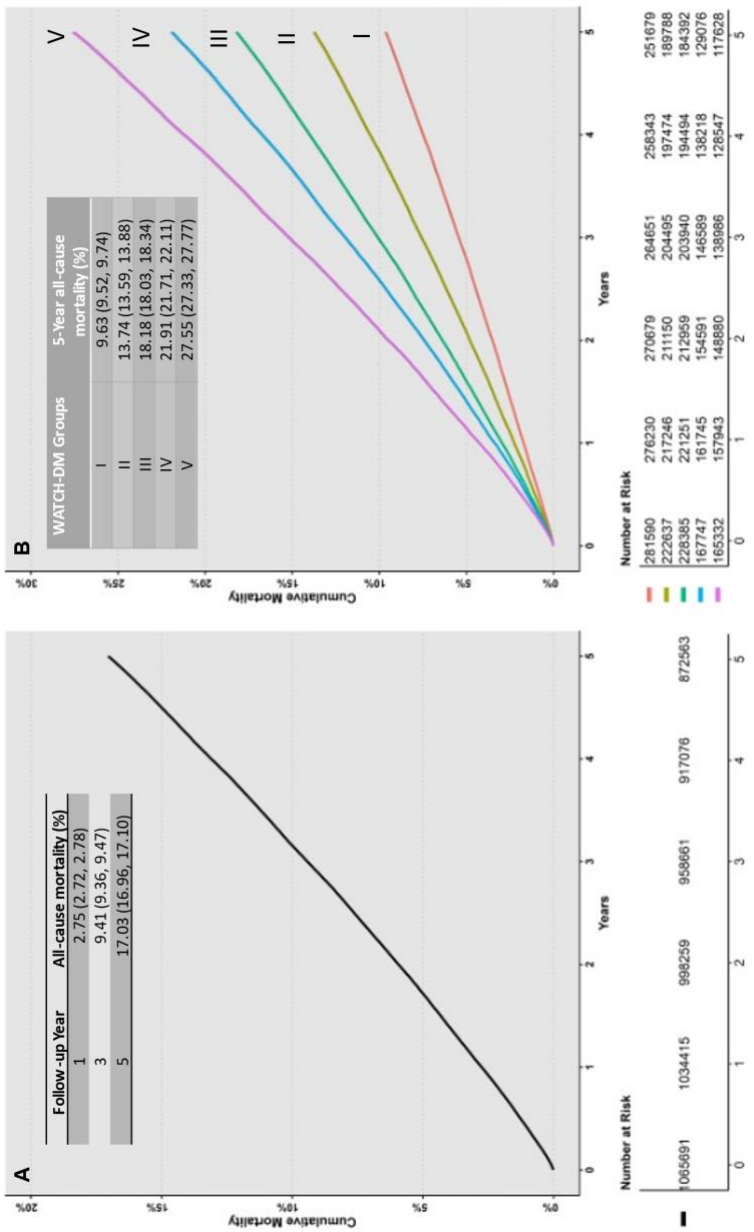
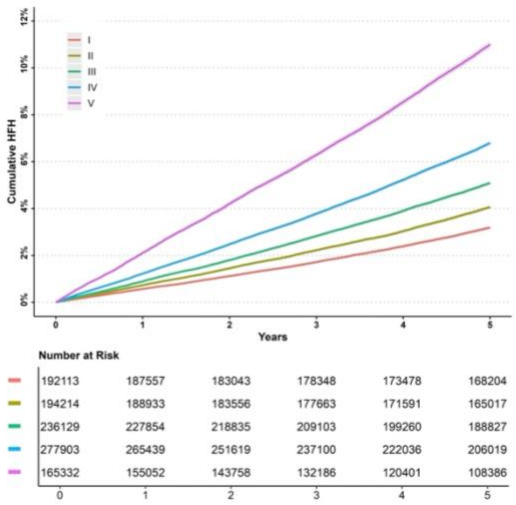


Figure 6-3. Cumulative 5-year all-cause mortality

Cumulative 5-year all-cause mortality, overall and according to the SDI quintile



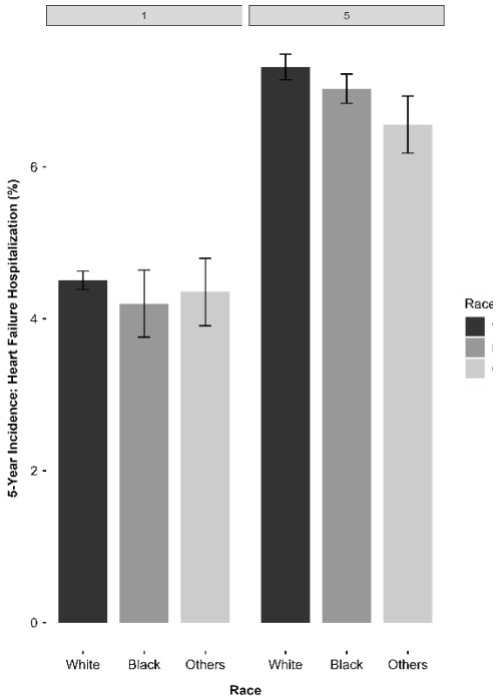
WATCH-DM Groups	Incident heart failure at 5 years (%)
I (Very low risk)	3.18 (3.10, 3.26)
II (Low risk)	4.06 (3.97, 4.15)
III (Moderate risk)	5.09 (4.99, 5.18)
IV (High risk)	6.80 (6.70, 6.90)
V (Very high risk)	11.00 (10.84, 11.16)

Figure 6-4. Cumulative 5-year heart failure hospitalisation according to the WATCH-DM score

This figure presents the cumulative 5-year heart failure hospitalisation according the WATCH-DM score

Among 1,065,691 patients, 180,383 died over the 5-year follow-up period, resulting in a cumulative mortality rate of 2.75 (95% CI: 2.72, 2.78) %, 9.41 (95% CI: 9.31, 9.47) % and 17.03 (95% CI: 16.96, 17.10) % at 1, 3 and 5 years respectively (Figure 6-3). After adjusting for age, the cumulative mortality rate for the whole cohort was 2%, 7.2% and 13.6% at 1,3, and 5 years respectively. The cumulative incidence of heart failure hospitalization for the whole cohort was 1.06%, 3.14% and 5.39% at 1, 3, and 5 years respectively. The cumulative incidence for 5-year heart failure hospitalization was incrementally higher with each subsequent WATCH-DM score group from 3.18% in group I to 11.00% in group V (Figure 6-4)(Table 6-4). We also observed that the relative risk for heart failure hospitalization increased for each subsequent group; considering group I as the reference group, those in group II had a 38% higher relative risk for heart failure hospitalization [HR 1.38 (95% CI:1.34, 1.42)], while it was more than three times higher in group V [HR 3.41 (95% CI: 3.32, 3.50)](Table 6-4). Harrell's c-statistic was 62.21 (61.84, 62.58) demonstrating modest overall discrimination.

The WATCH-DM score had acceptable calibration (E/O ratio = 1.02); although the GND test reported mis-calibration at the 95% confidence level (p-value < 0.001), the calibration plot showed that the overall calibration of the WATCH-DM score was acceptable (Figure 6-6).



SDI Quintile	Race	Observed 5-year HFH incidence (%)
1	White	4.50 (4.38, 4.62)
	Black	4.20 (3.75, 4.64)
	Others	4.35 (3.09, 4.79)
5	White	7.31 (7.14, 7.48)
	Black	7.03 (6.83, 7.22)
	Others	6.55 (6.18, 6.93)

Figure 6-5. Heart failure hospitalisation rates according to Race.

WATCH-DM score in the quintile of SDI: We linked zip code data from 1,012,315 patients (94.4% of the whole study cohort) with the Social Deprivation Index; 142,306 (14.05%) belonged to the least deprived quintile (Q1) while 191,619 (18.92%) belonged to the fifth quintile (Q5), the most deprived category. Patients in Q1 were much more likely to be White, while 38.3% of the patients in the SDI quintile 5 (most deprived) were black (Table 6-5).

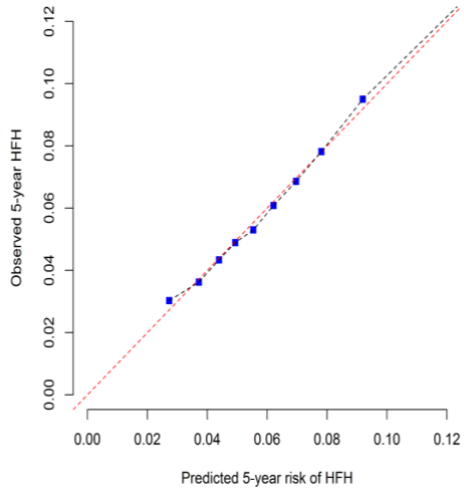
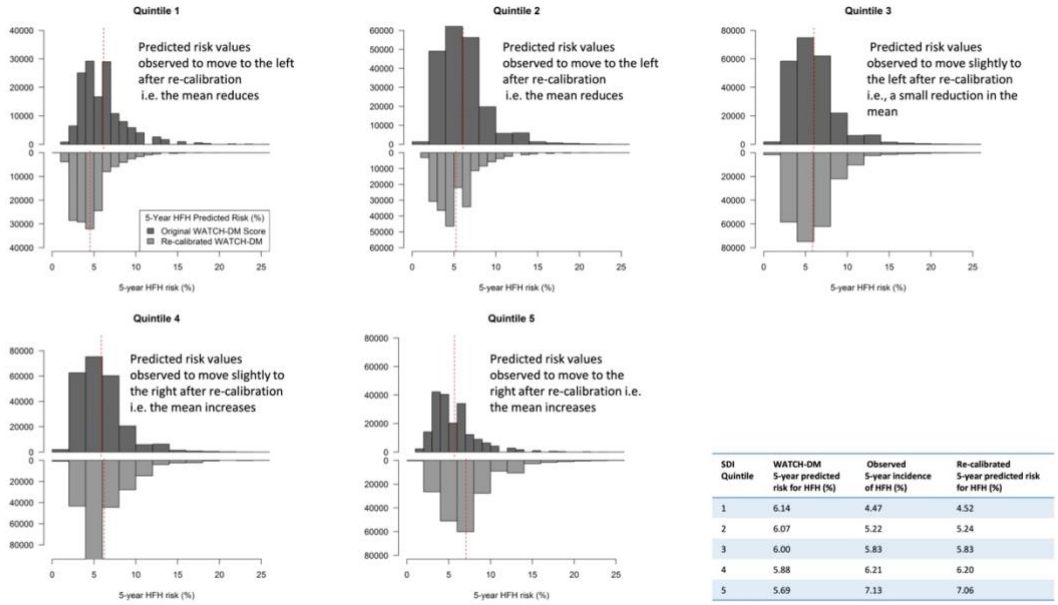


Figure 6-6. Calibration plot for the whole cohort

While the mean WATCH-DM score incrementally reduced from Q1 (mean:15.2, SD:3.6) to Q5 (mean:14.5, SD:3.7) of the SDI (Figure 6-2), we observed a gradual increase in the 5-year cumulative incidence for heart failure hospitalization across the quintiles of the SDI (Table 6-6). We observed that in quintiles 1 and 5 of the SDI, 5-year heart failure hospitalization rates did not differ much according to the patient's race (Figure 6-5). Including the SDI to the original WATCH-DM score improved model fit (SDI covariate p-value < 0.001; model coefficient 0.131). The model including both variables also reported lower AIC (1480283 vs 1478687) and BIC (1480292 vs 1478705) values. The Somers D_{xy} values were very similar in the test (0.2611) and train (0.2609) datasets on internal validation (100 bootstrapped samples). Compared to the null model (Brier score: 0.52) as well as the model including on the original WATCH-DM score (Brier score 0.51), the Brier score for the combined model was slightly lower (0.50) demonstrating improved discrimination.

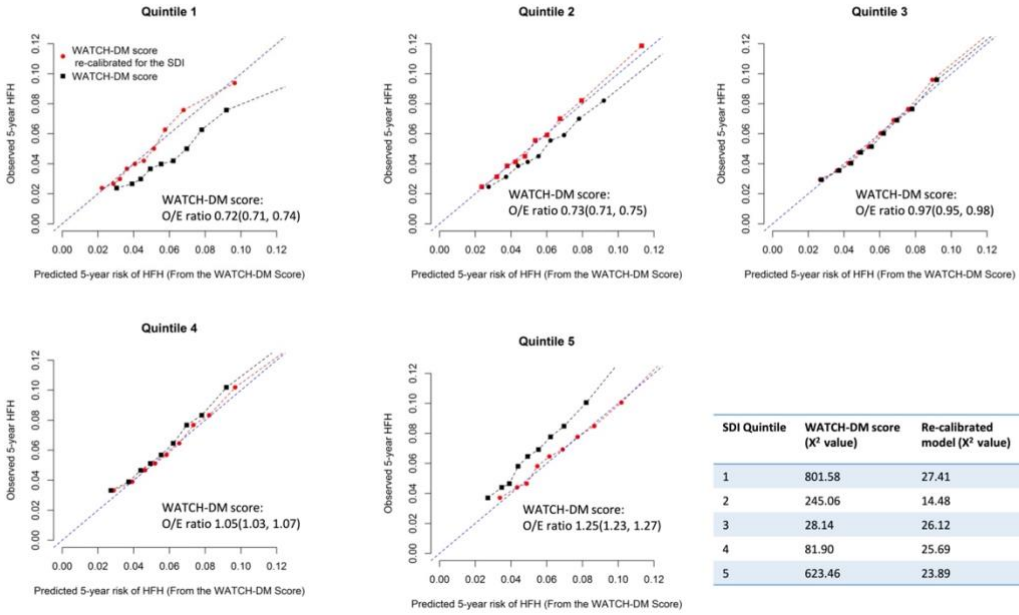


SDI Quintile	WATCH-DM 5-year predicted risk for HFH (%)	Observed 5-year incidence of HFH (%)	Re-calibrated 5-year predicted risk for HFH (%)
1	6.14	4.47	4.52
2	6.07	5.22	5.24
3	6.00	5.83	5.83
4	5.88	6.21	6.20
5	5.69	7.13	7.06

Figure 6-7. Histogram of the observed and predicted heart failure hospitalisation rates according to the SDI.

Predicted rates are in dark gray while observed rates are in lighter gray.

The discrimination (Harrell's c-statistic) for the WATCH-DM score across quintiles of the SDI was like that observed for the whole cohort. However, the WATCH-DM score was not well calibrated to predict the 5-year heart failure hospitalization across SDI quintile. As observed from the E/O ratio, while it over-predicted the risk in Q1 & 2, it under-predicted the risk in Q5. This is demonstrated by plotting the histogram for the original and recalibrated scores in Figure 6-7 and the calibration plots in Figure 6-8 (black line – original WATCH-DM score, red line – recalibrated WATCH-DM score). The chi-square value for the Greenwood Nam D'Agostino test was, therefore, also correspondingly high in each quintile (please refer to the table provided Figure 6-8). We recalibrated the WATCH-DM score using the correction factor (details provided in the supplement) and observed that the mean predicted risk reduced in Q1 (O/E ratio: 0.72) & Q2 (O/E ratio: 0.73) of the SDI, while it increased in SDI groups Q4 (O/E ratio: 1.05) & Q5 (O/E ratio; 1.25) (please refer to the table provided in Figure 6-7). After using the derived



SDI Quintile	WATCH-DM score (X^2 value)	Re-calibrated model (X^2 value)	P-value
1	801.58	27.41	0.001
2	245.06	14.48	0.1
3	28.14	26.12	0.001
4	81.90	25.69	0.002
5	623.46	23.89	0.004

Figure 6-8. Calibration plots for the original and recalibrated sdiWATCH-DM score

correction factor to recalculate the predicted risk, as depicted in Figure 6-8, we observed better calibration as reported by reduced chi-square values for the GND test and calibration plot lines (red vs black) that were closer to the ideal reference line. Using decision curve analysis, we also confirmed that the re-calibrated WATCH-DM score provided a potential 'net benefit' when used in clinical practice. After re-calibration, the predicted cumulative risk for heart failure hospitalization in the very high-risk group (WATCH-DM score $\geq$ 19) was 8.01% and 13.26% respectively in quintiles 1 (least deprived) and 5 (most deprived) of the SDI (Table 6-7).

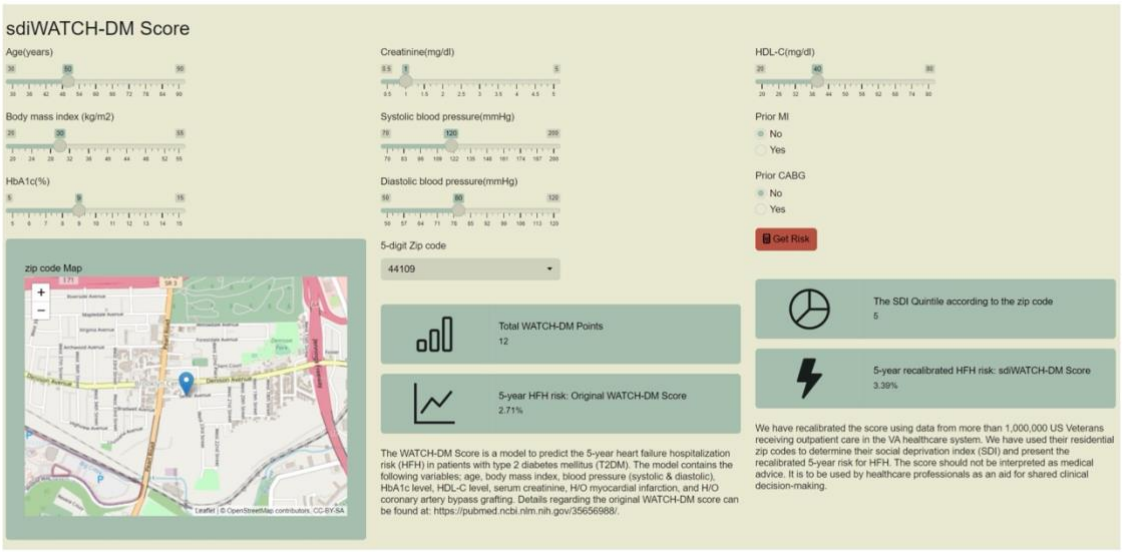


Figure 6-9. sdiWATCH-DM score online calculator

Online Calculator: We have packaged our results in an online calculator available at https://svd09.shinyapps.io/sdiWATCH-DM. Users can enter specific patient data including the residential zip code. This dashboard provides the SDI quintile for that zip code, the 5-year heart failure hospitalization risk according to the WATCH-DM Score and the re-calibrated 5-year heart failure hospitalization risk (Figure 6-9).

DISCUSSION

We externally validated the WATCH-DM score, a model that predicts 5-year incident heart failure hospitalization in patients with diabetes mellitus, in a large cohort of US Veterans. Our main finding is that beyond the original WATCH-DM score, the level of social deprivation (as measured by the SDI) is associated with the 5-year risk for heart failure hospitalization. In patients residing in least deprived ZIP codes, the WATCH-DM score overestimated observed risk, while it underestimated the risk in patients residing in the most

deprived ZIP codes. We provide readers with a recalibrated WATCH-DM score which accounts for SoDH and is available for clinical use via a simple online dashboard.

It is now known that social deprivation is associated with increased HF risk. In an earlier study, we reported that more socially deprived US counties had higher heart failure related mortality rates (Bevan et al., 2020). Data from the Southern Community Cohort Study demonstrated that each inter-quartile increase in neighbourhood deprivation index was associated with a 12% increase in risk of incident HF (Akwo et al., 2018). However, we feel that the association between social deprivation and cardiovascular diseases, including heart failure may be even stronger in patients with T2DM. In a cohort study of 900 patients investigating the association between the SDI and ischemic events after percutaneous coronary intervention, researchers found that the SDI was associated with increased risk for events only in patients with diabetes (adjusted HR for Q4 vs Q1 1.72 [1.01-2.92], P=0.04) but not in patients without T2D (P=0.39). A recent study from Sweden examined the association between neighbourhood-level social deprivation and HF risk specifically in patients with T2DM (Li et al., 2020). In this population study of 434,000 patients, authors reported that the adjusted risk of heart failure was higher in deprived neighbourhoods (HR for high deprivation vs low deprivation 1.11, 95% CI 1.06–1.16, in men & 1.15, 95% CI 1.09–1.21, in women). In our recently published study that examined this issue in US Veterans, we showed that SDI was associated with increased risk for the first heart failure hospitalization as well as recurrent events in T2DM patients (Deo et al., 2023a). In this analysis, we observed that despite a decline in the WATCH-DM scores across the SDI, the observed heart failure hospitalization rates increased. This fact further demonstrates that social deprivation influences the risk of heart failure hospitalization independently of the covariates present in the WATCH-DM score, specifically, age, BMI, glycaemic control, and kidney function. Together, this information supports the notion that social deprivation metrics influence heart failure risks that are not accounted for by the traditional cardiovascular risk scores.

This study adds to the emerging literature that focuses on social and environmental factors as determinants of residual risk in cardiovascular disease. Recent studies have focused on developing poly-social risk scores that augment the routinely included clinical and demographic factors (Figueroa et al., 2020). For example, Javed et al. developed and validated a poly-social risk score that included seven different SDoH domains and reported that it had good discriminatory capacity to predict atherosclerotic cardiovascular disease (Javed et al., 2021). Similarly, Zhao et al examined social risk and incident T2DM in the UK Biobank study and showed that a poly-social risk score (derived from three SDoH domains) could reliably predict incident T2DM (Zhao et al., 2022). Hence, these studies support our observations regarding the important role that SDoH play in determining cardiovascular risk.

Given the above discussion, it is thus important to investigate, and if necessary, recalibrate cardiovascular prediction models within the context of social deprivation. However, we observed in our review of current literature, as did others, that very few risk scores account for the social determinants of health. An observational cohort study of 100,000 patients in the US reported that the AHA/ACC pooled cohort equation, a model to predict the incidence of atherosclerotic cardiovascular disease, showed poorer discrimination (c-index 0.8 versus 0.7) in patients residing in deprived neighbourhoods (Akwo et al., 2018). Similar observations were also reported using data from Scotland (Kimenai et al., 2022). However, to our knowledge, our study is the first to recalibrate a well-validated prediction score based on neighbourhood social deprivation. Via this study, we further hope to demonstrate how including social deprivation measures may help to refine risk estimates produced by clinical risk scores. Recent efforts have developed poly-social risk scores, that incorporate multiple domains of SDoH and linked them with cardiovascular risk.

This also highlights the fact that socioeconomic factors mediate the HF risk through mechanisms other than those related to traditional risk factors included in the WATCH-DM score. We used a simple tool like the ZIP code to determine the SDI index. Zip codes are commonly available in electronic medical records

making our recalibrated risk model easy to use for practicing physicians. We have packaged our risk model into a tool that clinicians can routinely use on their phones. We hope that our study and application will encourage clinicians to use this score in the shared decision-making process with patients. It is also important to note that even a small improvement in model fit with the addition of SDoH can be considered 'socially meaningful', given that socioeconomic factors affect entire populations. Hence, the population impact of even a minor change in social deprivation burden can be significant. This speaks to the value of including social determinants in risk models not only from a statistical perspective, but also as key upstream constructs that shape more downstream diabetes and cardiovascular outcomes. Social factors are often ignored in traditional risk assessment, representing missed opportunities to understand their effects across the full cascade of cardiovascular disease development. Given the evolving data science approaches, capturing geospatial SDoH and environmental data in real time may aide in cardiovascular risk prediction[28]. These modified/recalibrated risk scores incorporating SDoH can help concentrate resources like community-based care programs and screening initiatives to those at the highest medical risk. Recently, the Center for Medicare and Medicaid Services introduced a new policy to incorporate SDoH data collection with the aim of promoting equitable healthcare access and delivery (Services, 2023). A recent review highlighted multiple missed opportunities in improving the care of people with T2D (Rajagopalan et al., 2021). Authors recommended a comprehensive patient evaluation as the first step towards providing high-quality diabetes care; our study clearly demonstrates that understanding the patients SDoH is an important part of such an evaluation.

Strength and Limitations: This study should be interpreted within the context of cohort limitation. First, our cohort is predominantly male, which is reflective of the VA population (although included numerically high number of women [n= 35432]). The relative predominance of men may limit generalization of the current findings to women, and additional external validation of the recalibrated model in a mixed gender population is thus required. Second, our cohort consists

of patients with diabetes mellitus that received outpatient care at VA medical centres; therefore, compared to a population-based cohort, our patients likely have a higher baseline risk. While this would impact the absolute event rate, it does not change the mis calibration that we observe across the SDI groups. Therefore, as a benchmark for readers to understand the absolute increase in heart failure hospitalization risk, we report both the original and recalibrated 5-year heart failure hospitalization in our `online risk calculator portal` (link provided in the manuscript). Third, social deprivation metrics at smaller area levels like census tracts may provide a more accurate measure for each patient. However, these measures are not available for routine use in clinical practice, while patient generally knows their residential ZIP code. ZIP code information is also readily available in other large databases like that provided by the Center for Medicare and Medicaid Services. We feel that although the census tract level SDI may be a more accurate marker, ZIP code level information is more applicable for routine use. Lastly, our definition for heart failure hospitalization is obtained from International Classification of Disease codes, not prospectively clinically adjudicated information. However, this will again, not impact the difference in heart failure rates seen across the spectrum of social deprivation. Importantly, we were able to externally validate the WATCH-DM risk model in a large real-world cohort. Our large geospatially coded cohort provided further proof that neighbourhood-level deprivation metrics can be helpful to refine risk estimates above and beyond clinical covariates. Adoptions of such measures in prediction models is likely to improve accuracy.

CONCLUSION

Our large external validation study using real-world data demonstrated that the WATCH-DM score is acceptable for use in a real-world cohort of patients with type 2 diabetes mellitus. We observed that the 5-year risk for incident heart failure hospitalization is modulated by social deprivation. To aid clinicians caring for this patient population we produced a simple-to-use online SDI recalibrated WATCH-DM calculator. Our study highlights the wider need to consider the social determinants of health in future risk prediction modelling.

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6.3 Appendix

Table 6-1. WATCH-DM Scoring system

This table presents the points for each covariate in the WATCH-DM score. Users obtain the total count for their patient and then use the lower table to see the 5-year predicted risk for heart failure. Definitions used in our cohort: Patients that had a prior history of myocardial infarction or coronary artery bypass grafting (CABG) were defined as prior MI and prior CABG respectively. For all laboratory tests (HbA1c, creatinine, HDL-C), the most recent values prior to the index date were selected. Age was calculated from the patients index date and birth date. Vital parameters (BMI, blood pressure) were obtained at the time of the index visit. If values were not available at the index visit, then the most recent value prior to the index visit was selected.

Variable included in the score	Category	Points allotted
Age (years)	< 50	0
	50 – 54	1
	55 – 59	2
	60 – 64	3
	65 – 69	4
	70 – 74	5
	≥ 75	6
Body mass index (kg/m^2)	< 30	0
	30 – 34	1
	35 – 39	3
	≥ 40	4
HbA1c (%)	< 7	0
	7 – 8.9	1
	9 – 9.9	4
	10 – 11.9	5
	≥ 12	6
Serum Creatinine (mg/dl)	< 1	0
	1 – 1.49	1
	≥ 1.5	3
High Density Lipoprotein Cholesterol	< 30	5
	30 – 59	3
	≥ 60	0
Systolic blood pressure (mm Hg)	< 100	0
	100 – 139	2
	140 – 159	4
	≥ 160	5
Diastolic blood pressure (mm Hg)	< 60	4

	60 – 79	2
	≥ 80	0
Prior myocardial infarction	Yes	3
Prior coronary artery bypass grafting	Yes	3

Table 6-2. WATCH-DM total points

This table presents the total number of points for each risk category in the WATCH-DM score. It also provides the predicted 5-year risk estimate for heart failure hospitalization based on the total points accrued by the patient.

Cumulative WATCH-DM points	Risk Category	5-year predicted Heart failure hospitalization risk
≤ 11	Very low	1.1 %
12 – 13	Low	2.8 %
14 – 15	Moderate	4.7 %
16 – 18	High	8.3 %
≥ 19	Very high	15.9 %

Table 6-3. Baseline Characteristics of the study cohort

	Overall	WATCH-DM Risk categories				
		I (Very low risk)	II (Low risk)	III (Moderate risk)	IV (High risk)	V (Very high risk)
		≤ 11	12 - 13	14 - 15	16 - 18	≥ 19
Patient count	1065691	192113	194214	236129	277903	165332
WATCH-DM score (mean (SD))	14.84 (3.67)	9.63 (1.51)	12.54 (0.50)	14.50 (0.50)	16.87 (0.80)	20.68 (1.86)
Age at index visit (years) (mean (SD))	67.45 (9.87)	59.69 (7.31)	64.23 (8.04)	68.29 (9.39)	71.05 (9.44)	73.01 (8.82)
Female sex	35432 (3.3)	17115 (6.1)	7196 (3.2)	5636 (2.5)	3205 (1.9)	2280 (1.4)
Race						
-White	805190 (75.6)	189892 (67.4)	166912 (75.0)	178773 (78.3)	133960 (79.9)	135653 (82.0)
-Black	173491 (16.3)	66009 (23.4)	36994 (16.6)	31560 (13.8)	21118 (12.6)	17810 (10.8)
-Others	87010 (8.1)	25689 (9.2)	18731 (8.4)	18052 (7.9)	12669 (7.5)	11869 (7.2)
Hispanic Ethnicity	66747 (6.3)	19554 (6.9)	14973 (6.7)	14377 (6.3)	9520 (5.7)	8323 (5.0)
Systolic blood pressure (mean (SD))	132.64 (16.83)	129.47 (14.25)	131.39 (15.84)	133.07 (16.94)	134.87 (18.13)	136.85 (19.22)
Diastolic blood pressure (mean (SD))	74.18 (11.06)	78.37 (9.86)	75.23 (10.37)	73.37 (10.77)	71.60 (11.14)	69.36 (11.36)
Coronary artery disease	330668 (31.0)	28125 (14.6)	40391 (20.8)	64581 (27.3)	102851 (37.0)	94720 (57.3)
Cerebrovascular disease	118783 (11.1)	13967 (7.3)	17296 (8.9)	25640 (10.9)	35450 (12.8)	26430 (16.0)
Peripheral arterial disease	159546 (15.0)	17604 (9.2)	22546 (11.6)	33138 (14.0)	47914 (17.2)	38344 (23.2)
Chronic kidney disease (eGFR < 60 ml/min/m^2)	140891 (13.2)	17447 (6.2)	20835 (9.4)	29252 (12.8)	29790 (17.8)	43567 (26.4)
Serum Creatinine (mg/dl) (mean (SD))	1.43 (1.01)	1.15 (0.69)	1.33 (0.91)	1.46 (1.03)	1.61 (1.15)	1.81 (1.25)
HbA1c level (mean (SD))	7.27 (1.35)	6.84 (0.98)	7.07 (1.15)	7.29 (1.30)	7.53 (1.47)	7.97 (1.73)
High-density lipoprotein level (mean (SD))	38.36 (18.89)	46.90 (22.65)	39.04 (17.21)	36.21 (15.79)	33.71 (15.48)	30.57 (15.01)
Chronic anemia	166055 (15.6)	23023 (12.0)	24099 (12.4)	34038 (14.4)	48452 (17.4)	36443 (22.0)
Dialysis dependent	22061 (2.1)	2438 (0.9)	3032 (1.4)	4494 (2.0)	4709 (2.8)	7388 (4.5)
Chronic liver disease	61867 (5.8)	14383 (7.5)	11931 (6.1)	12949 (5.5)	14257 (5.1)	8347 (5.0)
Arterial hypertension	910882 (85.5)	150131 (78.1)	159695 (82.2)	202311 (85.7)	246671 (88.8)	152074 (92.0)
Prior cancer	140648 (13.2)	18146 (9.4)	22385 (11.5)	32117 (13.6)	41758 (15.0)	26242 (15.9)
Chronic obstructive pulmonary disease	218107 (20.5)	38691 (20.1)	38395 (19.8)	47088 (19.9)	56929 (20.5)	37004 (22.4)

WATCH-DM score (mean (SD))	14.84 (3.67)	9.63 (1.51)	12.54 (0.50)	14.50 (0.50)	16.87 (0.80)	20.68 (1.86)

Table 6-4. Heart failure hospitalisation risk at 5 years according to WATCH-DM groups observed in our study cohort

WATCH-DM score group	5-year HFH rate	Hazard ratio (95% CI)	p-value
I (very low risk)	3.18 (3.10, 3.26)	Reference	-
II (low risk)	4.06 (3.97, 4.15)	1.28 (1.23, 1.32)	< 0.001
III (moderate risk)	5.09 (4.99, 5.18)	1.61 (1.56, 1.66)	< 0.001
IV (high risk)	6.80 (6.70, 6.90)	2.17 (2.11, 2.24)	< 0.001
V (very high risk)	11.00 (10.84, 11.16)	3.61 (3.50, 3.72)	< 0.001

Table 6-5. Baseline characteristics in our cohort according to the SDI

	SDI Quintile 1	SDI Quintile 5
Number of patients	142306	191619
Age at index visit (years) (mean (SD))	69.58 (9.87)	65.71 (9.87)
Female sex	3136 (2.2)	6597 (3.4)
Race		
-White	125224 (88.0)	100205 (52.3)
-Black	8348 (5.9)	73298 (38.3)
-Others	8734 (6.1)	18116 (9.5)
Hispanic Ethnicity	3322 (2.3)	18219 (9.5)
Systolic blood pressure (mean (SD))	132.02 (16.41)	133.11 (17.33)
Diastolic blood pressure (mean (SD))	73.00 (10.77)	75.14 (11.35)
Coronary artery disease	49379 (34.7)	50547 (26.4)
Cerebrovascular disease	15360 (10.8)	22155 (11.6)
Peripheral arterial disease	21408 (15.0)	29155 (15.2)
Chronic kidney disease (eGFR < 60 ml/min/m^2)	17952 (12.6)	27840 (14.5)
Serum Creatinine (mg/dl) (mean (SD))	1.42 (0.97)	1.40 (0.97)
HbA1c level (mean (SD))	7.17 (1.20)	7.39 (1.51)
High-density lipoprotein level (mean (SD))	38.76 (18.44)	39.09 (19.20)
Chronic anemia	20490 (14.4)	34166 (17.8)
Dialysis dependent	2783 (2.0)	4995 (2.6)
Chronic liver disease	7359 (5.2)	12479 (6.5)
Arterial hypertension	120757 (84.9)	165290 (86.3)
Prior cancer	20152 (14.2)	25269 (13.2)
Chronic obstructive pulmonary disease	25434 (17.9)	39918 (20.8)

Table 6-6. 5-year Heart failure hospitalisation rate for each SDI group

WATCHDM score group	HFH cumulative incidence (Overall)	Social deprivation index				
		Quintile1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
I (Very low risk)	3.18 (3.10, 3.26)	2.38 (2.17, 2.59)	2.65 (2.47, 2.82)	3.08 (2.90, 3.25)	3.46 (3.29, 3.64)	3.95 (3.75, 4.14)
II (Low risk)	4.06 (3.97, 4.15)	2.83 (2.62, 3.05)	3.57 (3.38, 3.77)	3.89 (3.70, 4.09)	4.36 (4.17, 4.56)	5.26 (5.02, 5.50)
III (Moderate risk)	5.09 (4.99, 5.18)	3.82 (3.60, 4.04)	4.31 (4.11, 4.50)	4.95 (4.75, 5.14)	5.39 (5.19, 5.60)	6.68 (6.43, 6.93)
IV (High risk)	6.80 (6.70, 6.90)	5.03 (4.80, 5.25)	6.05 (5.84, 6.26)	6.75 (6.54, 6.96)	7.36 (7.14, 7.58)	8.43 (8.16, 8.70)
V (Very high risk)	11.00 (10.84, 11.16)	8.33 (7.96, 8.71)	9.75 (9.41, 10.08)	11.11 (10.77, 11.45)	11.63 (11.27, 11.99)	13.77 (13.31, 14.21)

Table 6-7. Predicted 5-year heart failure hospitalisation risk after model recalibration

WATCH-DM Points	WATCH-DM Group	SDI Quintiles Risk for HFH at 5 years (%)				
		1	2	3	4	5
< 11	I (Very low risk)	2.22	2.60	2.93	3.17	3.71
12 - 13	II	3.06	3.59	4.05	4.39	5.19
14 - 15	III	3.85	4.51	5.09	5.15	6.50
16 - 18	IV	5.08	5.95	6.70	7.25	8.55
≥ 19	V	8.01	9.39	10.53	11.38	13.26

6.4 Author Declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	Impact of Residential Social Deprivation on Prediction of Heart Failure in Patients with Type 2 Diabetes: External Validation and Recalibration of the WATCH-DM Score Using Real World Data. Deo SV, Al-Kindi S, Motairek I, McAllister D, Shah ASV, Elgudin YE, Gorodeski EZ, Virani S, Petrie MC, Rajagopalan S, Sattar N. Circ Cardiovasc Qual Outcomes. 2024 Mar;17(3):e010166. doi: 10.1161/CIRCOUTCOMES.123.010166. Epub 2024 Feb 8. PMID: 38328913 SVD, YE – Louis Stokes Cleveland VA Medical Centre, Cleveland, USA SAK – Houston Methodist Hospital, Houston, USA IM, EZG, SR – University Hospitals, Cleveland, USA SV – Aga Khan University, Karachi, Pakistan ASVS – LSTHM, London, UK MCP, NS, DMA – University of Glasgow, Glasgow, UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	SVD, NS, DAM
Data Curation	SVD
Formal Analysis	SVD
Investigation	SVD
Methodology	SVD, ASVS, NS, DAM
Project Administration	NS, MCP
Visualisation	SVD
Writing - original draft	SVD, SAK, IM
Writing - review & editing	MCP,DAM, NS, SV, SR

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 7: Paper 6

7 The Time-varying Cardiovascular benefits of Glucagon like peptide-1 agonist therapy in patients with type 2 Diabetes Mellitus: Evidence from large multinational trials

7.1 Preface

Along with the initiation of GDMT, continued adherence to therapy is also important for patient outcome. While in the prior studies, I have done some work to outline factors that are associated with GDMT initiation/non-initiation, in this chapter, I demonstrate that continued therapy with GLP1-RA improves cardiovascular outcomes over a 4-year study period.

Published Manuscript

Citation

The time-varying cardiovascular benefits of glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus: Evidence from large multinational trials.

Deo SV, Marsia S, McAllister DA, Elgudin Y, Sattar N, Pell JP.Diabetes Obes Metab. 2022 Aug;24(8):1607–1616. doi: 10.1111/dom.14738. Epub 2022 May 23.
PMID: 35491516

Manuscript

ABSTRACT

Aims: As hazard ratios are often difficult to understand and interpret, we pooled data from eight contemporary cardiovascular outcomes trials (CVOT) of GLP1-RA drugs using restricted mean survival time (RMST) to evaluate their cardio-protective effect.

Material and methods: Data from eight multinational CVOT RCT's of GLP1-RA drugs for type 2 diabetes mellitus were pooled. Flexible parametric survival models were fit from published Kaplan Meier plots. The differences between arms in restricted mean survival time (ΔRMST) were calculated at 12, 24, 36 and 48 months. ΔRMST were pooled using an inverse variance weighted random effects model; heterogeneity was tested with the Cochran's Q statistic. The endpoints studied were: 3-point major adverse cardiovascular event (3-pt MACE), all-cause mortality, stroke, cardiovascular mortality, and myocardial infarction.

Results: We included eight large (3,183-14,752 participants; total = 60,080; median follow-up range: 1.5 – 5.4 years) GLP-1 RA trials. Among GLP-1RA recipients, we observed an average delay in 3-point MACE by 0.03, 0.15, 0.37 and 0.63 months at 12, 24, 36, 48 months respectively. At 48 months, while CV mortality was comparable in both arms [pooled ΔRMST 0.163 (-0.112, 0.437);

p=0.24], overall survival was higher [ΔRMST = 0.261 (0.08 – 0.43) months] and stroke was delayed [ΔRMST 0.22 (0.15 – 0.33)] in patients receiving GLP1-RA

Conclusions: GLP-1RA may delay the occurrence of MACE by an average 0.6 months at 48 months. This is easier for clinicians and patients to interpret than hazard ratios which assume a knowledge of absolute risk in the absence of treatment. Future analyses need to dissect out gains for patients with and without established CV disease.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health concern that leads to significant morbidity and mortality (Khan et al., 2020). The global prevalence of T2DM in 2030 is projected at 366 million (Wild et al., 2004). In the United States, atherosclerotic cardiovascular disease (ASCVD) is present in approximately 50% patients with T2DM; it is, in fact, the leading cause of death in people with T2DM (Weng et al., 2020) (Huang et al., 2001). Due to concern regarding the cardiovascular safety of rosiglitazone, since 2008, every new drug trial involving treatment for diabetes mellitus was required to undergo a cardiovascular safety evaluation (Regier et al., 2016). Cardiovascular outcome trials (CVOT) of sodium glucose co-transporter 2 inhibitors (SGLT2i) and then subsequently, glucagon like peptide 1 receptor agonists (GLP1-RA), while designed to ensure cardiovascular safety, have reported a significant reduction in adverse cardiovascular events. To date, 4 trials (LEADER, SUSTAIN-6, Harmony Outcomes, and Amplitude-O) of liraglutide, semaglutide, albiglutide and efpeglenatide respectively have demonstrated positive cardiovascular results (Gerstein et al., 2021, Marso et al., 2016b, Hernandez et al., 2018, Marso et al., 2016a) . A recent meta-analysis pooled data from eight large CVOT randomized trials (Sattar et al., 2021). On pooled analysis, these drugs led to a relative reduction in major adverse cardiovascular event (MACE) rates, cardiovascular mortality, and myocardial infarction by 14%, 12% and 11% respectively. In fact, both the European and American professional societies recommend that these

agents should be considered in all T2DM patients with ASCVD or at significantly elevated risk of ASCVD (Das et al., 2020, Cosentino et al., 2020).

Trials in medicine often attempt to enumerate the treatment effect over an observed time-period. Testing for, or assuming, proportional hazards and presenting the overall treatment effect as a hazard ratio (HR) is the traditional method for reporting results (Stensrud et al., 2019). However, HRs are difficult to interpret (Stensrud et al., 2019) and are meaningless without knowledge of the absolute risk of events over a given period of follow-up in the absence of treatment. Moreover, if the treatment is beneficial and delays the endpoint, the proportional hazards assumption may be violated (Stensrud et al., 2019). The restricted mean survival time (RMST) is the average survival time from the beginning to a specific time-point during the follow-up (Royston and Parmar, 2013). Importantly, the difference in the RMST (ΔRMST) between treatment arms is an easy, reliable, and model-free estimate of the treatment benefit expressed in a meaningful scale (Royston and Parmar, 2013). Depending on study design, it can also be presented in easily understood units of time (days, months, years). This measure has been adopted routinely to interpret and pool oncology trials (Pak et al., 2017). Although a recent randomized trial on the use of direct oral anticoagulants after valve replacement utilized RMST as their primary prespecified analytical method(Gupta et al., 2016), RMST is rarely applied to analysing cardiovascular drug trials. We, therefore, applied this method to help interpret the results of large multinational randomized controlled trials evaluating the cardiovascular benefits of GLP-1RA therapy. We calculated the difference in RMST between treatment and control arms at specific time points and pooled trial estimates using a random effect model. In doing so, we hope to demonstrate the feasibility and utility of applying the RMST method for producing effect estimates that are easier to understand and clinically interpret.

METHODS

A recent meta-analysis has already performed a thorough systematic review of available literature (Sattar et al., 2021). Hence, trials included in this paper were selected for analysis in our study. We further evaluated the full text of these trials to ensure that results were presented graphically as Kaplan Meier (KM) plots and not simply as hazard ratios (HR).

Post-hoc analyses of trials may not be adequately powered to evaluate secondary outcomes; therefore, they were excluded, even if they reported cardiovascular outcomes as their endpoints. The protocol for our meta-analysis was prospectively registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (ID - INPLASY202170097; doi: 10.37766/inplasy2021.7.0097). The study was conducted and reported according to PRISMA guidelines.

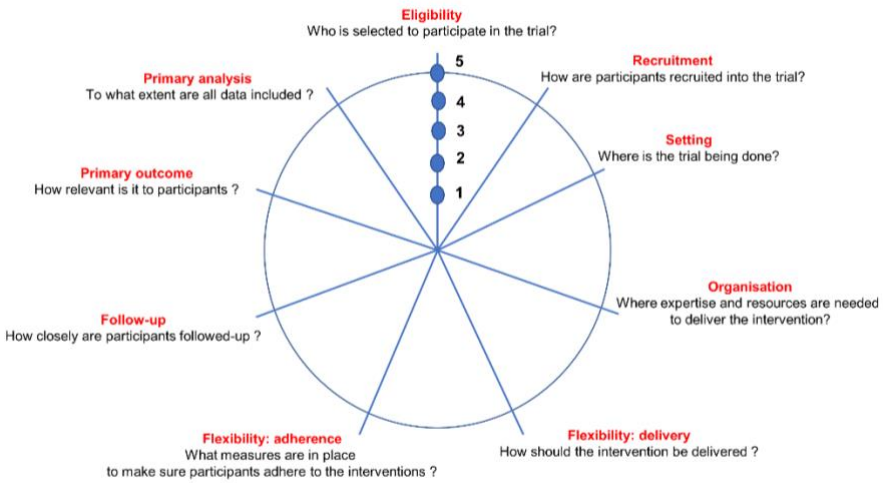

Figure 7-1. The PRECIS2 tool.

This figure presents the nine domains of the PRECIS2 tool with a score from 1-5 assigned to each domain.

Study Quality assessment: Study quality and bias were independently evaluated by two authors (SM, SVD) using the Cochran risk of bias tool and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria

respectively. The PRECIS-2 (Pragmatic Explanatory Continuum Indicator summary) tool, a set of 9 questions pertaining to study design, each scored on a 5-point scale, was used to evaluate whether the trial was more explanatory or more pragmatic in nature (Loudon et al., 2015) (Figure 7-1).

Selection of Endpoints:

The primary endpoint evaluated in seven trials was three-point major adverse cardiovascular event (3 pt-MACE), defined as a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. The ELIXA trial reported a 4-pt MACE (unstable angina, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke). Secondary endpoints evaluated in our study were cardiovascular mortality, all-cause mortality, stroke and myocardial infarction. The survival curves for the selected endpoints were collected from each eligible trial publication. The total number of patients randomized to each arm of the study, the number of patients at risk at specific time periods during the observation period and the total number of events in each arm were abstracted from the information provided in the manuscript.

Statistical Analysis:

The published survival curves were individually imported as large images into ScanIt, a digitizing software . Then the survival lines for each arm were traced and the corresponding co-ordinate data were abstracted. From this information, the survival curves were then reconstructed using the method described by Guyot et al(Guyot et al., 2012). Among tools available to obtain information from published Kaplan Meier (KM) curves, the Guyot method has been observed to be the most reliable (Wan et al., 2015). For each available trial endpoint, a flexible Royston and Parmar parametric model (PM) with 3 cubic spline terms and a time varying covariate (treatment arm) was fitted. Rather than using a fixed mathematical distribution like the exponential, Weibull, or log-normal models, using spline segments lends flexibility and allows for a more reliable fit to data, especially in the presence of non-proportional hazards. For each trial,

the model fit was evaluated by graphing the fitted parametric curve and the non-parametric Kaplan Meier curve together. Model fit using the flexible PM model were excellent, as depicted in S-figures 1. This was also observed at the tails of the distribution; therefore, we were able to reliably extrapolate trial effects beyond their original duration. Hence, in studies where data was not directly available, these flexible parametric models were utilized to obtain the ΔRMST. This mathematical modelling was performed with the assumption that the observed treatment effect was constant during the extended follow-up time durations. Using information generated from the fitted models, ΔRMST for all trials were obtained at 12-, 24-, 36- and 48-months follow-up for 3-pt MACE/4-pt MACE and at 24- and 48-months follow-up for the other endpoints. The ΔRMST derived from each trial were pooled using the Der-Simonian and Laird random effects method and inverse variance weighting used to obtained the overall estimate for each end-point. (DerSimonian and Laird, 1986) Inter-study heterogeneity was assessed using the I^2 index and Cochran´s Q test. I^2 index values $\leq$ 25%, 26-50% and > 50% indicated low, moderate, and high degrees of heterogeneity respectively, and Cochran´s Q statistic p<0·05 suggested significant heterogeneity. Statistical analyses were performed in R 4.0.2 (The R foundation for Statistical Computing). Packages used in analyses were – metafor (version 3.0-2)(Wolfgang, 2010) , metaRMST (version 1.1.0)(Isabelle Weir and 2021) and rstpm2 (version 1.5.2)(Mark Clements and Alessandro Gasparini 2021).

Sensitivity Analysis: Sensitivity analyses were performed using various methods. Firstly, ΔRMST were also calculated from the KM estimates (KM model) at the same time points and were pooled using the same random effects method. These two estimates (from the PM and KM models) were then graphed and visually compared for overlap, an indicator that both values were not statistically different from each other.

Secondly, our primary endpoint (3-pt MACE) was also re-analysed by excluding results of the ELIXA trial. Unlike the other trials pooled, ELIXA included only patients with acute coronary syndrome and used lixisenatide, a very short acting exendin-4 analogue. Both these aspects of trial design differ substantially from

all the other included studies. Thirdly, to evaluate the consistency between the absolute and relative effect estimates, semi-parametric Cox proportional hazards models were fit for each trial data at 24 and 48 months. From these models, the hazard ratio (HR) for the treatment versus control arm was calculated. The log transformed hazard ratios from each trial were then pooled using the Der Simonian-Laird random effects model with inverse variance weighting. We also repeated the analysis for 3-pt MACE/4-pt MACE selecting studies that primarily included participants with established stable ASCVD (> 85% having ASCVD at enrolment).

Lastly, for each trial and each studied endpoint, we calculated the ratio of the restricted mean time lost (RMTL) for the GLP-1RA vs the control group and abstracted the corresponding reported HR. These RMTL ratios and HR were separately pooled using a random effects inverse variance weighted model. Our observation that these two summary estimates are numerically quite similar further supports the validity of our ΔRST method.

Data Sharing Agreement:

No data sharing agreements were required because we extracted data from already published trials. Data sets containing information extracted from the published KM curves for each trial as well as the R code used for statistical analyses are provided in the supplemental sections with the manuscript.

RESULTS

Overview of included trials:

In our study, the ΔRMST for included endpoints were calculated from graphs published in 8 trials (totalling 60,080 participants) (Gerstein et al., 2019, Gerstein et al., 2021, Hernandez et al., 2018, Marso et al., 2016a, Marso et al., 2016b, Pfeffer et al., 2015, Holman et al., 2017, Husain et al., 2019). Study participation ranged from 3,183 (Semaglutide; Pioneer-6) to 14,752 (exenatide; EXCSEL). The prevalence of ASCVD was lowest in the REWIND trial (31%), while a large proportion of patients enrolled in all other studies had established stable ASCVD (range from 73% in the EXCSEL trial to 100% in Harmony Outcomes, Amplitude-O). Unlike other trials, ELIXA only enrolled patients with acute coronary syndrome (Pfeffer et al., 2015). The REWIND trial (dulaglutide)(Gerstein et al., 2019) and the Harmony Outcomes trial (albiglutide)(Hernandez et al., 2018) had the longest (median follow-up 5.4 years) and shortest (median follow-up 1.5 years) follow-up respectively.

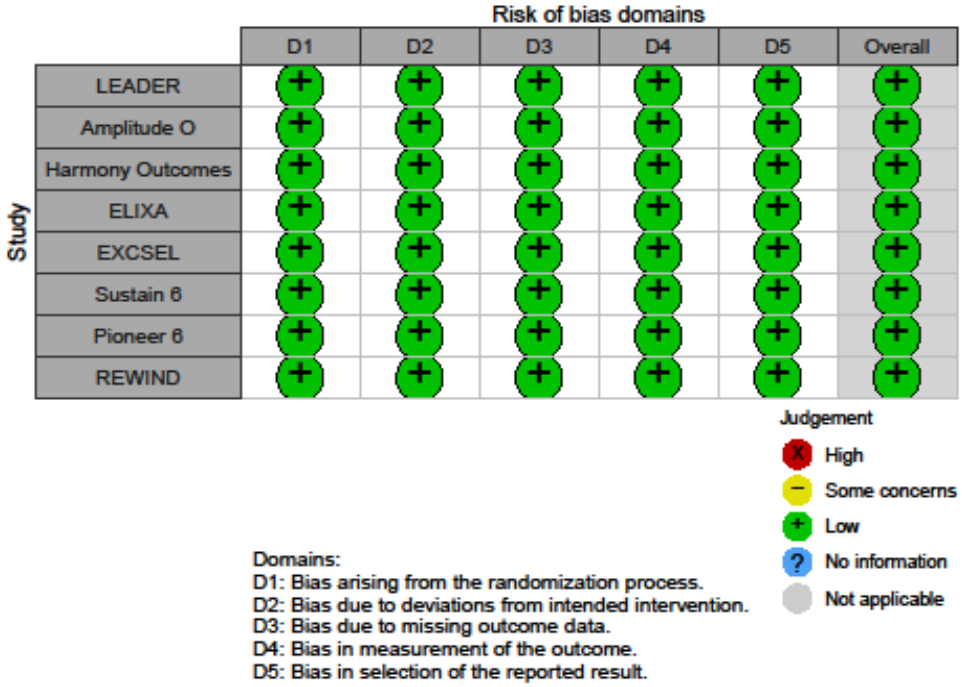

Figure 7-2. Risk of Bias analysis for each included study.

Completeness of follow-up in all trials was excellent (range from 97% - 100%). All trials were of high quality and free from significant bias (Figure 7-2). The eligible trials were also reasonably pragmatic in their study design. Using the PRECIS-2 tool, the pooled median score observed was 33.5/45. Every trial scored highly (4 or 5) for the following criteria: Trial setting, Primary analysis, and Primary outcome (Table 7-1). At enrolment, most patients were already being treated with angiotensin receptor blockers/angiotensin converting enzyme antagonists, statins, and appropriate anti-hypertensive agents. During the study period, in the Amplitude-O and Pioneer 6 trials, 15% and 10% patients also concomitantly received SGLT2 inhibitors.

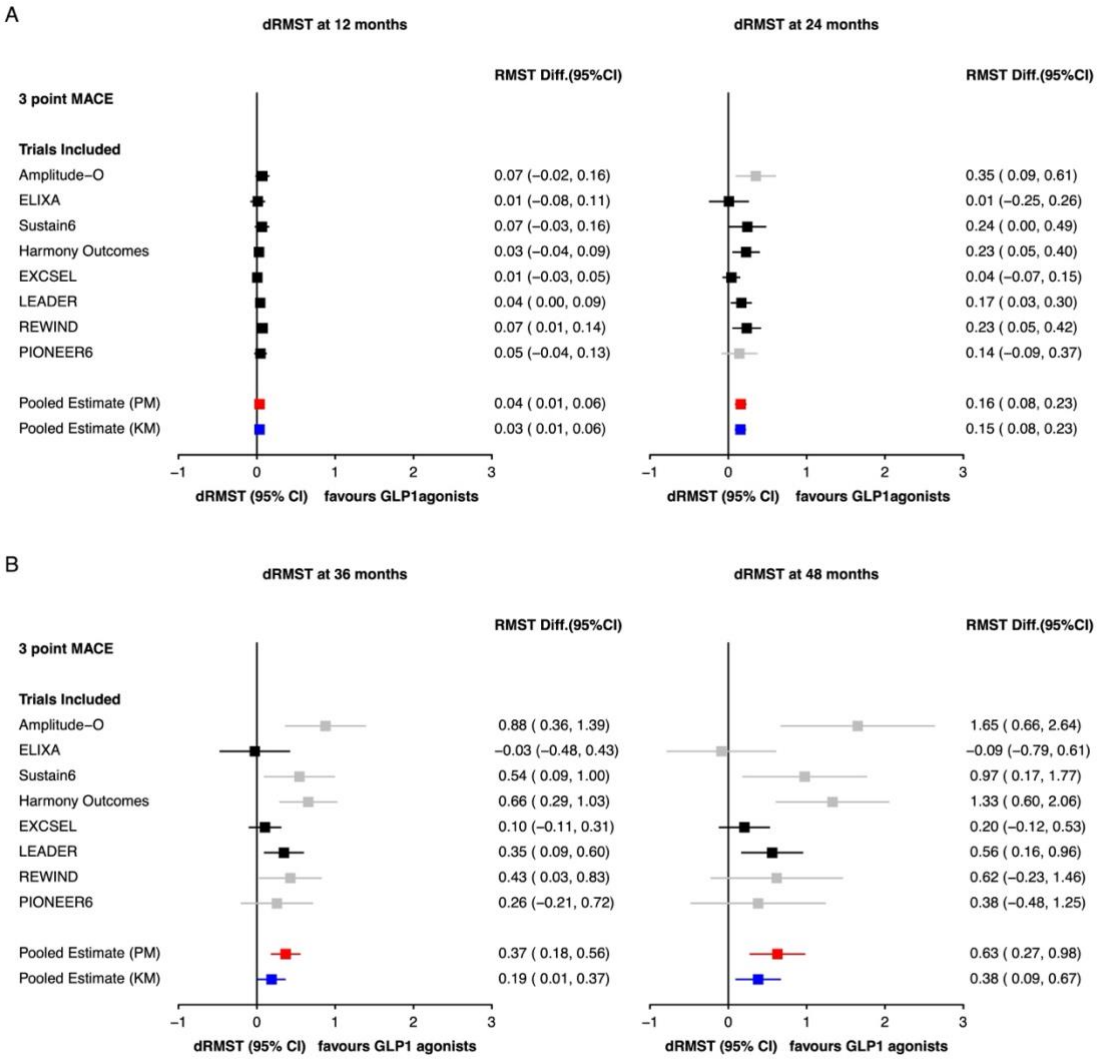

Figure 7-3. 3-point MACE / 4-point MACE.

These panel of forest plots present the ΔRMST for each trial and the pooled estimate obtained using the parametric method (red) and the Kaplan and Meier method (blue). Gray = ΔRMST calculated from extrapolated data; black = ΔRMST calculated directly from trial data.

3-point/4-point MACE:

All studies provided information regarding 3-pt MACE/ 4-pt MACE. (Table 7-2). On pooling data from these trials, using the PM method, we observed that, compared to the control arm, in participants receiving GLP1-RA drugs, this endpoint was delayed by 0.03(0.01 – 0.05), 0.15(0.08 – 0.23), 0.36(0.18 – 0.56) and 0.62(0.27 – 0.98) months at 12, 24, 36, 48 months respectively (Figure 7-3) While we observed minimal heterogeneity over short follow-up periods (12, 24

months), significant inter-study heterogeneity was observed by 36 (p-value = 0.03) and 48 months (p-value = 0.01) months follow-up. After excluding the ELIXA trial, at 48 months, pooled ΔRMST further increased to 0.72 (0.34 – 1.1) months (p < 0.001) favouring GLP1-RA drugs. Individually, among trials, ΔRMST was largest in the Amplitude-O (efpeglenatide) trial (1.65 months) followed by the Harmony Outcomes (albiglutide) trial (1.33 months). On limiting the analysis to studies (Harmony Outcomes, PIONEER 6, AMPLITUDE-O) that enrolled ≥ 85% patients with established ASCVD, we observed an even greater benefit in the cohort receiving GLP1-RA drugs [pooled ΔRMST = 1.1 (0.39 – 1.82); p = 0.002 at 48 months](Table 7-3). These results were supported by findings observed using direct KM integration (Figure 7-3). We also observed a non-linear increase in the benefit of GLP1-RA drugs over time. While ΔRMST was 0.03 (0.01 – 0.056) after 12 months of GLP1-RA therapy, this increased to 0.368 (0.178 – 0.558) and 0.627 (0.270 – 0.984) at 36 and 48 months respectively (Figure 7-4).

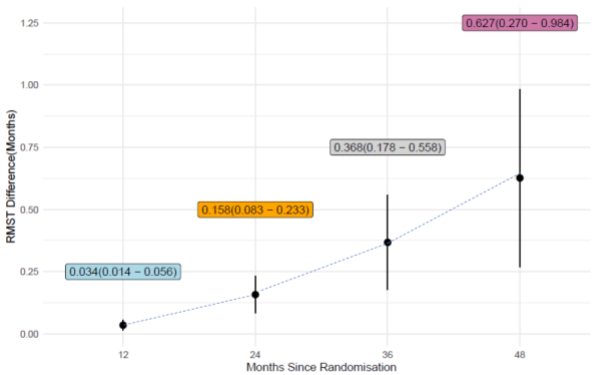

Figure 7-4. Non-linear benefit across follow-up time

This figure presents the ΔRMST for 3-point/4-point MACE obtained by pooling all eight trials. As depicted in the figure, the benefit of GLP1-RA drugs is non-linear across time.

Stroke:

The cumulative stroke rates were pooled from 5 studies (PIONEER 6, SUSTAIN-6, EXCSEL, REWIND and Harmony Outcomes). At 48 months, time to stroke was

delayed in patients treated with GLP1-RA [pooled ΔRMST 0.22 (0.15 – 0.33); p < 0.001)] (Figure 7-5).

Myocardial infarction:

Data regarding myocardial infarction were pooled from 4 trials (Sustain-6, REWIND, Harmony Outcomes, LEADER). At 48 months follow-up, we observed a small delay in the occurrence of myocardial infarction in patients treated with GLP-1RA drugs [0.42 (-0.02, 0.85); p = 0.06]; however, we also observed substantial heterogeneity in our model (I^2 = 75%; p = 0.01) (Figure 7-5).

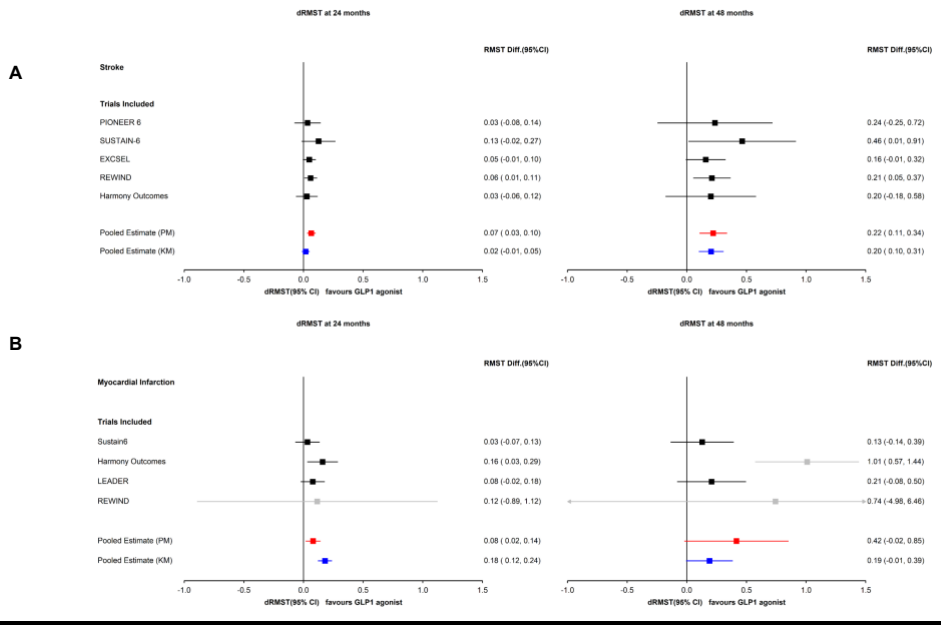

Figure 7-5. Stroke and Myocardial infarction.

These panel of forest plots present the ΔRMST for trials for the endpoints of stroke (A) and myocardial infarction (B). The pooled estimates obtained using the parametric method (red) and the Kaplan and Meier method (blue) are also presented. Gray = ΔRMST calculated from extrapolated data; Black = ΔRMST calculated directly from trial data.

Cardiovascular mortality:

Cardiovascular mortality was reported in 6 trials (Sustain 6, Harmony Outcomes, EXSCEL, LEADER, REWIND, Pioneer-6). At 48 months follow-up, CV mortality was not significantly different in both arms [pooled ΔRMST 0.163 (-0.112, 0.437); p =

0.24] (Figure 7-6). This was corroborated by the sensitivity analysis. We observed moderate between study variation (I^2 59% at 24 months; p = 0.01; I^2 56% at 48 months; p = 0.04) for our pooled model.

All-cause mortality:

All-cause mortality estimates were pooled from 2 trials (LEADER, EXCSEL). On pooled analysis, at 48 months, we observed increased survival in patients receiving GLP1-RA [pooled ΔRMST = 0.261 (95% CI 0.08 – 0.43) months (p < 0.001)] (Figure 7-6).

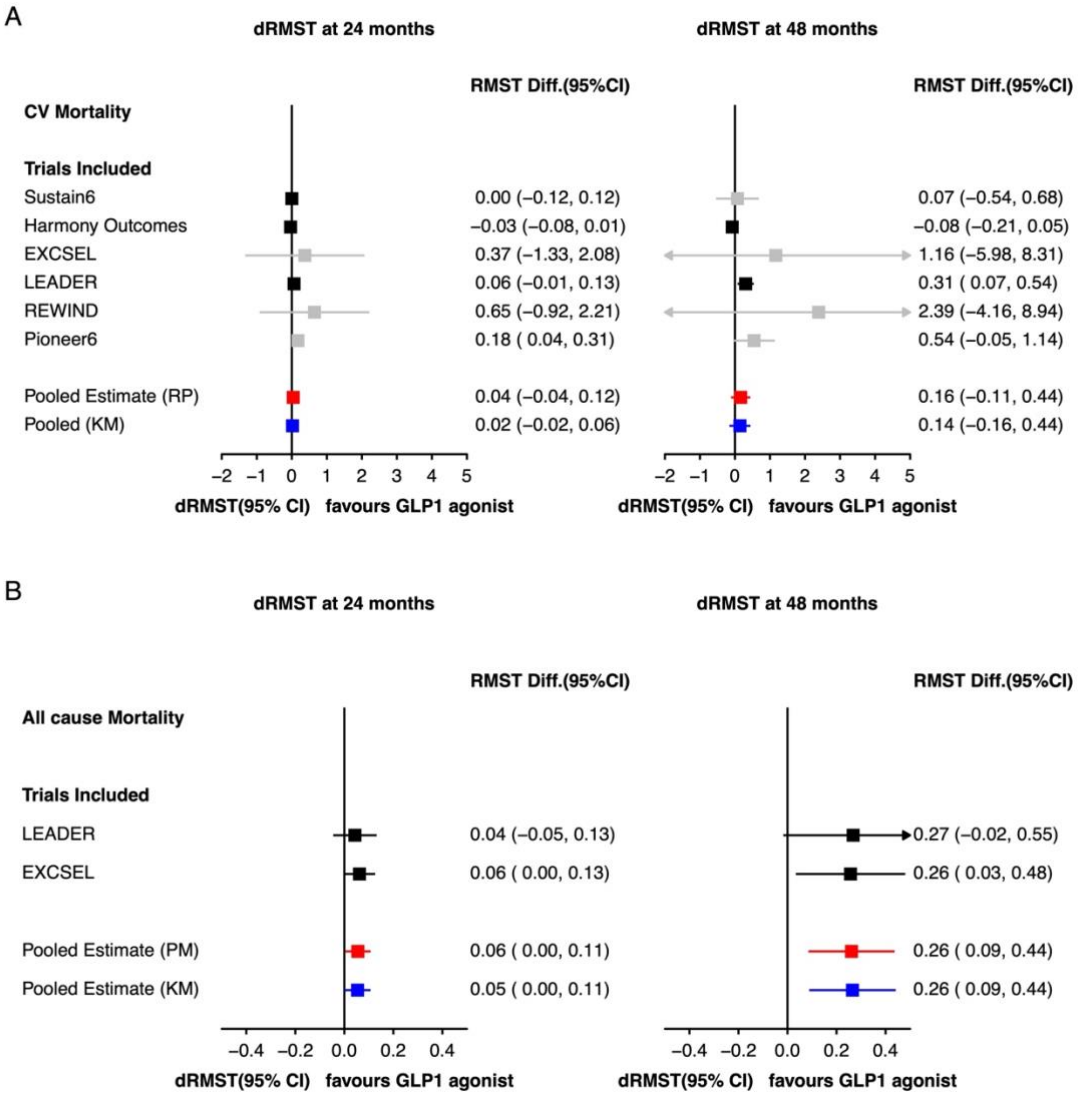

Figure 7-6. CV mortality and all-cause mortality.

These panel of forest plots present the ΔRMST for trials for the endpoints of CV mortality (A) and all-cause mortality (B). The pooled estimates obtained using the parametric method (red) and the Kaplan and Meier method (blue) are also presented. Gray = ΔRMST calculated from extrapolated data; Black = ΔRMST calculated directly from trial data.

Sensitivity Analyses:

A graphical comparison of the PM and KM models and for each endpoint, we observed that these summary estimates were quite similar. Pooled HR and RMTL

ratios for each endpoint were also quite similar (Figure 7-7). Both analyses support our main findings. Individual RMST values (at maximal follow-up) for each study arm are provided in Table 7-4.

DISCUSSION

Overview of salient findings: We used a novel application of an existing method to analyse and pool time-to-event data from large multinational cardiovascular outcome trials of GLP1-RA drugs in patients with type 2 diabetes mellitus. Using published Kaplan Meier graphs, we fit parametric models to each trial; calculated the difference in RMST between study arms (ΔRMST) and pooled trial these using the Der-Simonian and Laird inverse weighting random effects model. We determined that at 48 months follow-up, there was a significant delay in the occurrence of 3-point MACE among GLP-1RA patients; equivalent, on average, to an additional 0.6-month freedom from 3-point MACE. Among GLP-RA treated patients, we also observed a delay in the occurrence of stroke (pooled evidence from 5 trials), and possibly, all-cause mortality, although this result was based on data from only two trials. In GLP-1RA treated patients, we also report a 15% relative risk reduction in the occurrence of 3-point MACE at 12 months post randomization, an observation, that remained consistent during the 48 months follow-up.

Our results in context: Prior meta-analyses have reported the beneficial cardiovascular effects of GLP-1RA drugs in patients with type 2 diabetes mellitus based on hazard ratios (Kristensen et al., 2019, Giugliano et al., 2019). Sattar et al, recently pooled the hazard ratio of these eight multinational large trials and reported a 14% and relative risk reduction for 3-part MACE. This figure is difficult to interpret without knowing the absolute risk of MACE without treatment and how this varies over time.

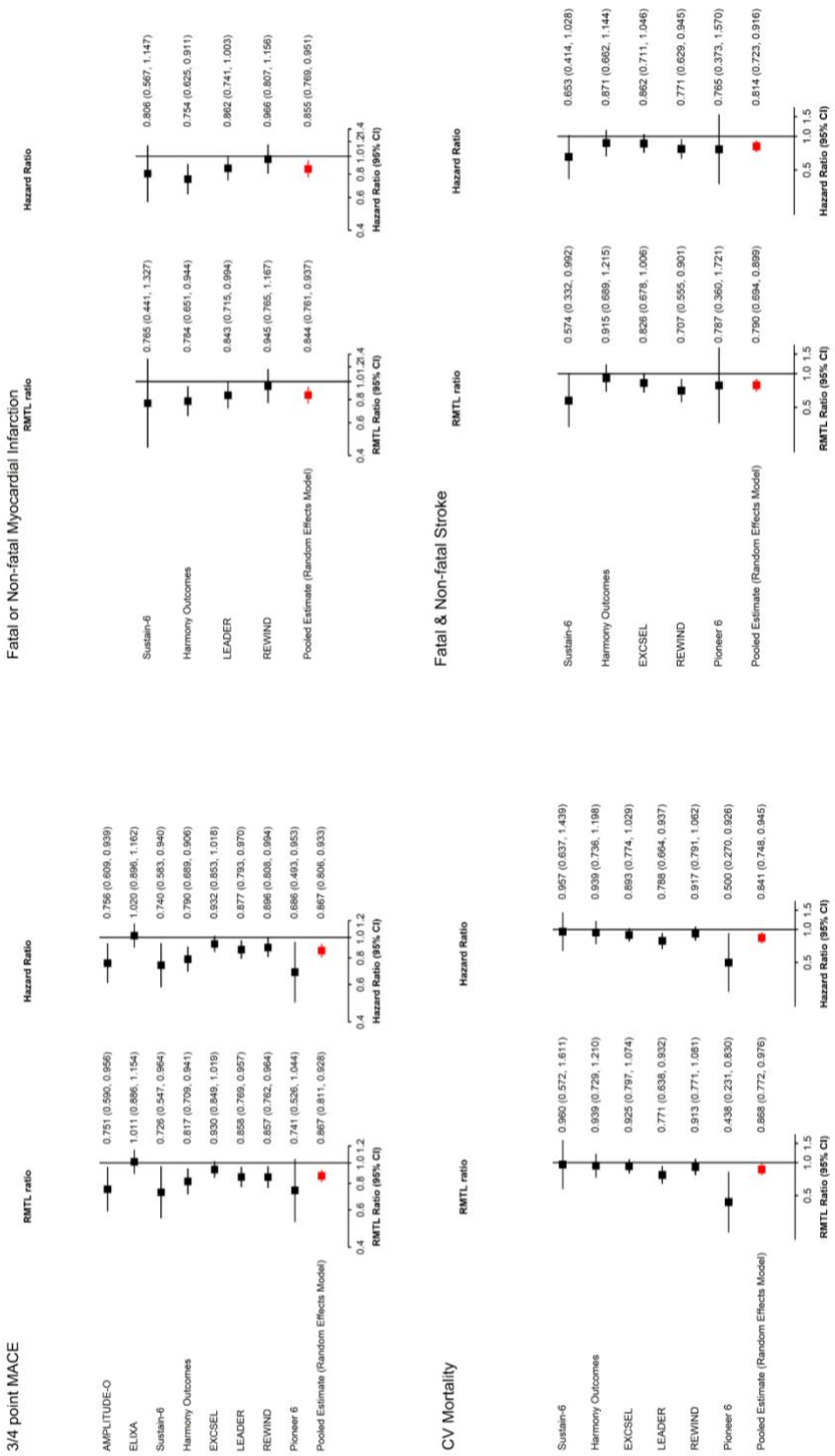

Figure 7-7. Restricted mean time lost (RMTL) and Hazard ratios (HR) compared.

This panel of forest plots compares the pooled RMTL and HR compared for each studied endpoint. Results demonstrate that these values are numerically very similar.

Therefore, it is of limited utility in reaching informed decisions in the context of a clinical consultation. In contrast, an average gain of 0.6 months over 4 years is easy for patients and clinicians to understand and discuss. Although this may appear modest, a large proportion in the control arm were on guideline directed medical therapy including DPP4i or SGLT2i. Re-analysis of 15 heart failure trials using RMST also reported similarly small positive effects (Perego et al., 2020). However, they continued use of these drugs was found to increase benefit. We too observed a non-linear benefit in the use of GLP1-RA with an 80% increase in ΔRMST from 36 to 48 months. While, at present, data are sparse, this demonstrates that continued use of GLP1-RA drugs may lead, over time, to significant increases in event-free survival.

We agree that substantial heterogeneity was observed in some pooled analyses. This may be due to several reasons. Firstly, it is still unclear at present if all GLP-1RA drugs provide similar cardiovascular benefits. Among randomized trials, to date, a positive cardiovascular benefit has been observed in the trials using albiglutide, dulaglutide, Semaglutide, liraglutide and efpeglenatide. All these agents, apart from efpeglenatide, are GLP-1RA homologues. Amplitude-O (efpeglenatide) is, in fact, the first trial, where an exendin-4 analogue has demonstrated a positive cardiovascular effect. Kristensen et al argued that earlier trials with exendin-4 agents (EXCSEL, ELIXA) failed to demonstrate CV benefits due to pharmacologic differences (short acting nature of exenatide) or poor drug adherence (40% permanent treatment discontinuation with lixisenatide) (Kristensen et al., 2019). Secondly, this heterogeneity may be due to differences in participant characteristics among trials. Trials enrolled a varying proportion of patients with established cardiovascular disease. If it becomes possible to gain individual participant data from all eight trials, it would be of interest to determine to what extent gains differ by baseline ASCVD or CKD status.

Clinical Implications: Traditionally, meta-analyses of time-to-event outcomes are performed by pooling reported hazard ratios from included studies. While this method is valid for dichotomous events, trials often have variable study

durations. Participants are also observed for differing time periods. Therefore, although simple, this method does not consider the possibility of a time-varying relationship between study and control arms. The reliability of HR also depends upon fulfilling the proportional hazards assumption, which is more challenging when multiple studies with variable time periods are combined. ΔRMST, being an absolute measure, is not dependent upon the proportional hazards assumption and can be calculated for any time point within the study duration. Recent data suggests that using RMST rather than HR may lead to improved study design with a possible reduction in study sample size.

In our study, we present results using an absolute summary estimate (ΔRMST). As a sensitivity analysis, we compare RMTL ratios and HR for our primary outcome, and both methods provide the similar overall inference. Absolute and relative measures provide complementary information for understanding data (Akobeng, 2005). Relative risk measures do not incorporate the baseline hazard; hence, relative risks often appear artificially inflated when compared to the absolute summary estimates calculated from the same data. Absolute measures, on the other hand, adjust for the baseline hazard in the study population, and provide a clearer understanding of the treatment effect. Another measurement often presented is the number needed to treat (NNT). While NNT is derived from the absolute risk reduction (ARR) and hence, also an absolute measure, a randomized trial reported that this is less clearly understood by patients (Sheridan et al., 2003).

We have followed guidelines provided by the National Institute of Healthcare and Excellence regarding study extrapolation (Latimer, 2013). Furthermore, by adopting a flexible parametric modeling approach, we have successfully captured the true observed effects in each trial (S-figure 1 & 2). The maximum extrapolated duration (24 months) was utilized for data in the Amplitude-O trial, while for all other trials, it was largely less than 12 months. While this method has been often applied to assess the economic benefit and quality adjusted life years gained in the study of cancers, it has rarely been implemented in the study of cardiovascular trials (Perego et al., 2020). As Perego et al discuss (Perego et

al., 2020), cost, practical complexities and need for rapid evidence generation often lead to limitations in our ability to extend trials beyond a certain period. Therefore, correctly applied, these methods can be used to obtain reliable, model-free estimates of the delay in adverse events observed in studies. Studies have also demonstrated that RMST ratios are consistent to conventional hazard ratios (Kloecker et al., 2020) (Perego et al., 2020). A recent study reported the use of the RMST to evaluate the lifetime benefit of dapagliflozin in the treatment of heart failure patients (Ferreira et al., 2020). Therefore, we believe that increasing the use of ΔRMST as a reported measure will provide clinicians with meaningful estimates to understand study results. We believe that this, in turn, will promote more informed decision-making and increase treatment adherence.

Strengths and Limitations: We agree that our study has certain limitations. In the absence of access to individual trial data, we have abstracted information from published Kaplan Meier curves. However, we have implemented a well validated, highly sensitive method to do so. Importantly, our choice of using the RMST as the effect estimate is more reliable and accurate than pooling reported hazard ratios. We agree that extrapolation of trial data by fitting parametric models may either under- or over-estimate treatment effects. However, using the flexible parametric model allowed us to capture the varying trajectory of each study arm. As demonstrated in the supplemental figures depicting model fit, we were able to accurately and reliably fit models to each trial data. We also performed sensitivity analyses with the KM method to support findings obtained from the parametric models. We were unable, in our study, to include all trial endpoints as KM curve information is essential for calculating ΔRMST.

CONCLUSION

Our pooled meta-analysis of 8 large randomized CVOT trials on GLP-1RA, corroborate previous findings that, as a class, these agents have significant cardiovascular benefits. Furthermore, we determined that, on average, treatment with GLP-1RA may delay the occurrence of major adverse

cardiovascular events by an average 0.6 months over a four-year period, potentially greater in trials where all participants had existing ASCVD. Whether such gains increase linearly or perhaps accelerate with longer use of GLP-1RAs remains to be established.

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7.2 Appendix

Table 7-1. PRECIS-2 score for each included study

Trials Included	Eligibility	Recruitment	Setting	Organization intervention	Flexibility-Delivery	Flexibility-Adherence	Follow up	Primary outcome	Primary analysis	Total
LEADER	4	4	5	2	4	3	2	5	4	38
REWIND	4	5	5	3	4	4	5	5	5	40
Sustain-6	4	4	5	3	2	3	5	5	4	35
Pioneer-6	4	4	5	3	2	3	5	5	4	35
ELIXA	4	4	5	2	2	3	5	5	5	33
EXCSEL	1	4	5	3	2	3	5	5	5	33
AMPLITUDE-O	4	5	5	3	2	2	2	5	5	38
Harmony-Outcomes	4	5	5	3	2	3	5	5	5	37

Table 7-2. Brief overview of included studies

This table presents a brief overview of the included studies. CC – control cohort; SC – study cohort

	EXCSEL (n = 14,752)	**ELIXA (n = 6,068)**	**LEADER (n = 9,340)**	**Sustain-6 (n = 3,297)**	**REWIND (n = 9,901)**	**Harmony Outcomes (n = 9,463)**	**Pioneer 6 (n = 3,183)**	**AMPLITUDE-O (n = 4,076)**
Year Study published	2017	2015	2016	2016	2019	2018	2019	2021
Drug Studied	Exenatide	Lixisenatide	Liraglutide	Semaglutide	Dulaglutide	Abiglutide	Semaglutide (oral)	Efpeglenatide
Pharmacology	Exendin-4 analogue	Exendin-4 analogue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	GLP-1 homologue	Exendin-4 analogue
Median/Total-follow-up time	3.2 (2.2 – 4.4) years / 5 years	25 months / 38 months	3.5 years / 54 months	2.1 years / 109 weeks	5.4 (5.1 – 5.9) years / 6 years	1.5 years / 28 months	15.9 (0.4 – 20) months / 86 weeks	1.81 (1.69 – 1.98) years / 24 months
Established ASCVD	73%	100%	81%	83%	31%	100%	85%	89.6%
Endpoints included in our analysis	3 pt-MACE, CV mortality, All-cause mortality	3 pt-MACE	3 pt-MACE, CV mortality, All-cause mortality, Myocardial infarction	3 pt-MACE, CV mortality, Myocardial infarction	3 pt-MACE, CV mortality, Myocardial infarction	3 pt-MACE, CV mortality, Myocardial infarction	3 pt-MACE	3 pt-MACE
Event rate for primary outcome (per 100 patient-years) (SC/CC)	3.7 / 4	6.4 / 6.3	3.4 / 3.9	3.24 / 4.4	2.35 / 2.66	4.57 / 5.87	2.9 / 3.7	3.1 / 5.9
Completeness of follow-up	98.8%	98.9%	99.7%	99.6%	97.1%	99.3%	100%	99.9%
Participants that	96.2 %	96.2%	96.8%	-	-	-	99.7%	-

complete d the trial

Table 7-3. Pooled Estimates for all reported endpoints

Reported endpoint	Time period	Pooled estimate (RP model)
3-pt / 4-pt MACE	12 months	0.04 (0.01, 0.06)
	24 months	0.16 (0.08, 0.23)
	36 months	0.37 (0.18, 0.56)
	48 months	0.63 (0.27, 0.98)
excluding ELIXA		
3-pt / 4-pt MACE	48 months	0.72 (0.34 – 1.1)
Limiting analysis to only studies that enrolled ≥ 85% patients with ASCVD, namely, Harmony Outcomes, PIONEER 6, AMPLITUDE-O		
3-pt / 4-pt MACE	12 months	0.042 (-0.001,0.086)
	24 months	0.23 (0.107,0.353)
	36 months	0.589 (0.259, 0.919)
	48 months	1.1 (0.39, 1.82)
All-cause mortality	12 months	0.01 (-0.003, 0.244)
	24 months	0.053(0.003, 0.107)
	36 months	0.139 (0.033, 0.245)
	48 months	0.261 (0.085, 0.437)
CV Mortality	12 months	0.009(-0.013,0.033)
	24 months	0.04(-0.037,0.12)
	36 months	0.093(-0.066,0.253)
	48 months	0.163(-0.112,0.437)
Myocardial infarction	12 months	0.016(-0.004,0.038)
	24 months	0.084(0.018,0.143)
	36 months	0.218(0.01,0.425)
	48 months	0.416(-0.02,0.853)
Stroke	12 months	0.013(0.002,0.24)
	24 months	0.052(0.02,0.085)
	36 months	0.119(0.055,0.183)
	48 months	0.204(0.11,0.341)

Table 7-4. RSMT at the maximal follow-up in each arm of the study

	Study	GLP1-RA studied	Maximal follow-up	RMST: GLP1-RA arm	RMST: Control arm
3-point MACE	AMPLITUDE-O	Efpeglenatide	24 Months	22.87 (22.74, 23.01)	22.58 (22.36, 22.80)
	ELIXA	Lixisenatide	38 Months	35.71 (35.34, 36.08)	35.76 (35.39, 36.13)
	Sustain-6	Injectable Semaglutide	109 Weeks / 27.25 Months	26.09 (25.90, 26.28)	25.75 (25.53, 25.98)
	Harmony Outcomes	Albiglutide	28 Months	25.19 (25.05, 25.33)	24.89 (24.74, 25.04)
	EXCSEL	Exenatide	60 Months	54.72 (54.39, 55.05)	54.33 (53.99, 54.68)
	LEADER	Liraglutide	54 Months	50.07 (49.74, 50.39)	49.40 (49.05, 49.75)
	REWIND	Dulaglutide	72 Months	67.72 (67.34, 68.10)	66.99 (66.58, 67.40)
	Pioneer 6	Oral Semaglutide	86 Weeks / 21.5 Months	21.01 (20.89, 21.14)	20.84 (20.69, 20.99)
CV mortality	Sustain-6	Injectable Semaglutide	109 Weeks / 27.25 Months	26.70 (26.60, 26.81)	26.69 (26.58, 26.80)
	Harmony Outcomes	Albiglutide	28 Months	26.43 (26.34, 26.51)	26.4 (26.31, 26.48)
	EXCSEL	Exenatide	60 Months	57.77 (57.57, 57.97)	57.62 (57.41, 57.83)
	LEADER	Liraglutide	54 Months	52.43 (52.24, 52.61)	52.03 (51.81, 52.25)
	REWIND	Dulaglutide	72 Months	69.29 (69.02, 69.57)	69.08 (68.80, 69.36)
	Pioneer 6	Oral Semaglutide	86 Weeks / 21.5 Months	21.06 (21, 21.12)	20.91 (20.82, 21.01)
All-cause mortality	LEADER	Liraglutide	54 Months	50.55 (50.32, 50.78)	50.21 (49.96, 50.45)
	EXCSEL	Exenatide	60 Months	57.09 (56.85, 57.32)	56.69 (56.44, 56.94)
Non-fatal Myocardial infarction	Sustain-6	Injectable Semaglutide	109 Weeks / 27.25 Months	26.57 (26.43, 26.71)	26.44 (26.28, 26.59)
	Harmony Outcomes	Albiglutide	28 Months	25.96 (25.8, 26.07)	25.76 (25.65, 25.87)
	LEADER	Liraglutide	54 Months	51.97 (51.73, 52.20)	51.61 (51.35, 51.86)
	REWIND	Dulaglutide	72 Months	68.77 (68.54, 69.01)	68.68 (68.45, 68.92)

Stroke	Pioneer 6	Oral Semaglutide	86 Weeks / 21.5 Months	21.05 (20.99, 21.11)	21.01 (20.95, 21.08)
	Sustain-6	Injectable Semaglutide	109 Weeks / 27.25 Months	25.33 (25.23, 25.42)	25.16 (25.04, 25.29)
	EXCSEL	Exenatide	60 Months	59.34 (59.17, 59.50)	59.10 (58.91, 59.28)
	REWIND	Dulaglutide	72 Months	70.83 (70.64, 71.02)	70.40 (70.16, 70.63)
	Harmony Outcomes	Albiglutide	28 Months	26.74 (26.66, 26.82)	26.70 (26.62, 26.79)

7.3 Author Declaration & Contribution Statement

Full paper citation, incl. authors and their affiliation	The time-varying cardiovascular benefits of glucagon-like peptide-1 receptor agonist therapy in patients with type 2 diabetes mellitus: Evidence from large multinational trials. Deo SV, Marsia S, McAllister DA, Elgudin Y, Sattar N, Pell JP.Diabetes Obes Metab. 2022 Aug;24(8):1607-1616. doi: 10.1111/dom.14738. Epub 2022 May 23. PMID: 35491516 SVD, YE, – Louis Stokes Cleveland VA Medical Center, Cleveland USA SM – Dow Medical College, Karachi, Pakistan DAM, NS, JP, SVD – University of Glasgow, Glasgow UK

Please state your author contribution below for each category in accordance with the principles of the Contributor Roles Taxonomy system (CRediT). Please refer to the descriptors of each category before completion (https://credit.niso.org/)

Conceptualisation	SVD, JP, NS, DMA
Data Curation	SD
Formal Analysis	SD
Investigation	SD
Methodology	SD, JP, NS, DMA
Project Administration	JP, NS
Visualisation	SD
Writing – original draft	SD, SM
Writing – review & editing	JP, NS,YE, DMA

We declare that the author contribution statements, in accordance with the CRediT system, are an accurate representation for this chapter/paper:

As per University guidelines, the primary supervisor and author signature block has been removed from this public version.

Chapter 8

8 Research in a Wider Context

8.1 Future ASCVD burden

My review of the existing literature and the studies that I conducted clearly demonstrate that a small proportion of ASCVD and CABG patients receive GDMT to prevent recurrent MACE events. Despite studying patients from a rich, developed country, social determinants such as race/ethnicity, median income, and residential location continue to impact the likelihood of patients receiving GDMT. Findings I observed in my work were mirrored by other research from other developed nations. Unfortunately, updated reports from the Global Burden of Disease consortium state that the ASCVD burden is expected to increase multi-fold globally (Chong et al., 2024). Apart from the impact of these predictions on developed nations, sadly, ASCVD rates are forecasted to increase at even higher rates in poor and developing nations in Asia and Africa (Chong et al., 2024). The Prospective Urban Rural Epidemiological Study is a prospectively developed cohort of people enrolled from 628 urban and rural communities in countries across the wealth spectrum (Walli-Attaei et al., 2022). In a subgroup analysis of 5060 participants from this cohort, the use of anti-platelet drugs (25.3%), beta-blockers (17.4%), statins (14.6%) and RAASI (19.5%) was dismal (Yusuf et al., 2011). Additionally, 69.3% and 80.2% of participants received no cardiovascular protective medications in lower middle- and low-income countries respectively (Yusuf et al., 2011). While the use of expensive therapies like PCSK9i, GLP1-RA or SGLT2i may be out of reach for some individuals, a large proportion of drugs that comprise GDMT for ASCVD patients are generic and inexpensive, even in poorer countries. In 2013, the Global CVD Taskforce brought together national organisations such as the American Heart Association, American College of Cardiology, European Society of Cardiology, European Heart Network, and the World Heart Federation to envisage their goal of `25 by 25`, i.e., a 25% global reduction in non-communicable disease mortality by 2025 (PMID: 26748650). The World Health Organisation conducted a survey of 32 generic medications used to treat chronic disease in six low-middle income countries (Bangladesh, Malawi, Nepal, Brazil, Pakistan and Sri Lanka) and reported a low availability of generic cardiovascular drugs in the public healthcare system (Dugani and Gaziano, 2016) (Cameron et al., 2011). Hence,

global citizenship and collaborative trans-continental efforts are needed to promote cardiovascular health and reduce the global ASCVD burden projected in the future.

8.2 What I learnt during my PhD

My primary motivation for enrolling in a PhD program was to work with excellent researchers in a more formal manner. I am a middle-career practicing cardiovascular surgeon and have always been interested in clinical outcomes research since my fellowship at the Mayo Clinic, Rochester between 2009 and 2012. Thereafter, I have tried to continue my research work (to the best of my ability) alongside a busy clinical practice. While continuing to expand my knowledge of cardiovascular disease, I am particularly interested in the application of newer statistical methods to obtain meaningful answers to my research questions. During this PhD I was fortunate to have the opportunity to learn from my excellent supervisors at the University of Glasgow. In this time period, I was able to further expand my biostatistical and epidemiological skills. This PhD endeavour (for me) was more to fulfil my joy of learning. I am delighted to exchange thoughts and ideas with collaborators and every supervisory meeting was an encounter that I thoroughly enjoyed. It also helped to balance my life and take me away from the stress and expectations of surgical clinical work.

Appendices

Glossary

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