MONASH University

The use and outcomes of anti-hyperglycaemic agents in people with type 2 diabetes

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BPharm(Hons)

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Doctor of Philosophy

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Contents

Abstract

Anti-hyperglycaemic agents (AHAs) play a critical role in preventing complications and death in people with Type 2 Diabetes Mellitus (T2D). In recent years, there has been an exponential rise in the dispensing of several AHA classes, so there is a need to examine patterns and predictors of use. In addition, the prevalence of T2D is high among older people, many of whom are frail. Since older and more frail people are at an elevated risk of adverse events from certain AHAs, it is critical to understand whether such individuals are receiving AHAs with the most favourable risk-benefit profile. The overall aim of this PhD project is to explore the use and outcomes of AHAs in the Australian population, using real-world data.

First, a study was conducted to determine which AHAs are dispensed as initial treatment for people with T2D. This study utilised a 10% sample of the Pharmaceutical Benefits Scheme (PBS). Results showed that 86% of Australians who received their first AHA were dispensed metformin monotherapy, and 5% received a sulfonylurea. Men and people with fewer comorbidities were more likely to initially receive >1 AHA, which is not specifically recommended in Australian clinical practice guidelines.

Subsequently, the National Diabetes Services Scheme (NDSS) dataset, linked to the PBS, was used to investigate treatment dynamics among people initiating a first-line AHA during the first year of use. This database included >85% of Australians diagnosed with diabetes. Approximately 23% of people initiating either metformin or a sulfonylurea received an addition or a switch within one year, with sulfonylurea

initiators receiving the addition or switch more rapidly. It was also found that older individuals and those with more comorbidities were less likely to receive additions, regardless of whether they initially received metformin or a sulfonylurea. Therefore, clinicians may be more cautious about adding or changing AHAs for people who are older or less robust.

Older and more frail individuals benefit less from stringent glycaemic targets and can suffer adverse events such as hypoglycaemia when treated with sulfonylureas or insulin. Using the Eastern Health (EH) dataset, we were able to determine that people with higher, versus lower levels of frailty were 35% less likely to be discharged from hospital with combinations of insulin and non-insulin AHAs, compared to no AHAs. This may indicate that hospital clinicians recognise that frail people with T2D require less intensive glycaemic targets.

It has previously been unclear whether frail individuals derive similar benefits from sodium-glucose cotransporter-2 inhibitors (SGLT-2Is), compared to the general T2D population. In a study conducted using hospital data from the state of Victoria, Australia, SGLT-2Is were found to reduce the 12-month risk of a major cardiovascular event by approximately 50%, compared to dipeptidyl peptidase-4 inhibitors, regardless of individuals' frailty levels.

The results obtained from PhD project will contribute to essential activities such as understanding the extent to which T2D clinical practice guidelines are implemented, as well as to improving the quality use of medicine, particularly with respect to vulnerable subpopulations of people with T2D.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Publications during enrolment

Wood, S.J., et al., *Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?* Diabetic Medicine, 2020. 37(8): p. 1367-1373.

Wood, S.J., et al., *Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012–2016.* The Journal of Frailty & Aging, 2021.

Buyadaa, O., … **Wood, S.J.,** … et al., *Can patterns of medication use explain the increasing incidence of end stage kidney disease among people with diabetes in Australia?* Diabetes Research and Clinical Practice, 2021. 172.

Stasinopoulos, J., **Wood, S.J.,** … et al., *Potential Overtreatment and Undertreatment of Type 2 Diabetes Mellitus in Long-Term Care Facilities: A Systematic Review.* J Am Med Dir Assoc, 2021.

Conferences during enrolment

- 2020: Oral Presentation at Australian Association of Gerontology (AAG) conference (via Zoom): *Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012-2016*
- 2019: Oral Presentation at Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) conference in Queenstown, New Zealand: *Treatment Dynamics in People who Initiate Metformin or Sulfonylureas for Type 2 Diabetes Mellitus*
- 2019: Oral Presentation at Australian Pharmaceutical Science Association (APSA) conference in Melbourne: *Treatment Dynamics in People who Initiate Metformin or Sulfonylureas for Type 2 Diabetes Mellitus*
- 2019: Oral Presentation at Asian Conference on Pharmacoepidemiology (ACPE) in Kyoto, Japan: *Treatment Dynamics in People who Initiate Metformin or Sulfonylureas for Type 2 Diabetes Mellitus*
- 2018: Oral Presentation at ACPE in Xi'an, China: *Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?*
- 2018: Oral Presentation at ASCEPT conference in Adelaide: *Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?*

Thesis including published works declaration

This thesis contains the following published works in Chapters 2 and 4, respectively:

Wood, S.J., et al., *Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?* Diabetic Medicine, 2020. 37(8): p. 1367-1373.

Wood, S.J., et al., *Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012–2016.* The Journal of Frailty & Aging, 2021.

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals and two submitted publications. The core theme of the thesis is the use and outcomes of anti-hyperglycaemic agents in people with type 2 diabetes in Australia. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Centre for Medicine Use and Safety, within the Faculty of Pharmacy and Pharmaceutical Sciences of Monash University, under the supervision of Dr. Jenni Ilomäki and Prof. Dianna Magliano (OAM). The inclusion of co-authors reflects the fact that the work came

from active collaboration between researchers and acknowledges input into team-based research.

In the case of *Chapters 2 through 5,* my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
2	Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?	Published	50%. Data analysis, writing first draft, applying feedback from co-authors	J.I. input into manuscript, assistance with data analysis, conceptualisation of research question 25% S.B. Input into manuscript, conceptualisation of research question 12.5% D.J.M. Input into manuscript, conceptualisation of research question 12.5%	N N N
3	Treatment Dynamics in People who Initiate Metformin or Sulfonylureas for Type 2 Diabetes Mellitus: A Cohort Study	Returned for revision from Therapeutic Advances in Drug Safety. Responses to reviewer comments have been submitted.	55%. Data analysis, writing first draft, applying feedback from co-authors	J.I. input into manuscript, assistance with data analysis, conceptualisation of research question 20% S.B. Input into manuscript, conceptualisation of research question 10% D.J.M. Input into manuscript,	N N N

				conceptualisation of research question 10% J.S. Input into manuscript 5%	 N
4	Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012–2016	Published	50%. Data analysis, writing first draft, applying feedback from co-authors	J.I. input into manuscript, assistance with data analysis, conceptualisation of research question 20% S.B. Input into manuscript, conceptualisation of research question 12.5% D.J.M. Input into manuscript 12.5% M.C. Input into manuscript (2.5%) L.F. Assistance with access to the dataset and initial setup and data cleaning (1.25%) C.K. Initial stages of data analysis (1.25%)	N N N N Y N
5	Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors and Dipeptidyl	Submitted to Diabetes Care.	58%. Data analysis, writing first draft, applying	J.I. input into manuscript, assistance with data analysis, conceptualisation	N

	Peptidase-4 Inhibitors in Frail People with Diabetes		feedback from co-authors	of research question 19% S.B. Input into manuscript, conceptualisation of research question 12% D.J.M. Input into manuscript 8% J.E.S. Expert guidance 2% M.C. Input into manuscript 1%	 N N N

Abbreviations J.I. Dr. Jenni Ilomäki, D.J.M Prof Dianna Magliano (OAM), S.B Prof J. Simon Bell, J.S Prof Jonathan Shaw, M.C. Prof Matteo Cesari, L.F. Dr. Laura Fanning, C.K. Claire Keen

I have not renumbered sections of published papers in order to generate a consistent presentation within the thesis.

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I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Dr. Jenni Ilomäki

Main Supervisor signature: **Date:** 3/8/2021

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Next, I owe a huge debt of gratitude to CMUS director Prof. Simon Bell, who has assisted me in conceptualising diabetes research questions which are likely to be both achievable and impactful. Simon has the “Midas touch” when it comes to writing and I have learned so much from him about how my own scientific writing can be made more concise and specific. I appreciate the opportunity that Simon has provided me in offering me the position of Postdoctoral Researcher at CMUS and look forward to continuing to contribute to high quality research outputs.

I would like to thank the co-authors who have provided excellent guidance including Prof. Jonathan Shaw and Prof. Matteo Cesari. As senior and well-renowned clinicians, your insightful feedback greatly improved the final manuscripts, and I am extremely thankful for your contributions. Thanks also to Claire Keen, whose coding set the foundation for Chapter 4 of this thesis, and to Dr. Laura Fanning, who conducted data cleaning and facilitated our access to the Eastern Health Dataset.

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From my first day at CMUS, I knew it was a good fit for me, as I could see that I was surrounded by welcoming, thoughtful, and collaborative people. Thank you to all CMUS PhD candidates, and colleagues, past and present, who I have had the pleasure of getting to know including Louise, Amanda, Michelle, Amy, Mouna, Natali, Sam, Kate W, Esa, Claire, Katrina, Kate P, Helena, Gopi, Monica, George, Laura, Nawar, Stella, Rehan, Katelyn and Renas. I have been very fortunate to work with such a great group of friendly and talented people. To the “long haulers” Jacqui,

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List of Abbreviations

AACE American Association of Clinical Endocrinology

ACCORD Action to Control Cardiovascular Risk in Diabetes

ACE American College of Endocrinology

ACEI Angiotensin Converting Enzyme Inhibitor

ACS Acute coronary syndrome

AD Alzheimer's disease

ADA American Diabetes Association

ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

AHA Anti-hyperglycaemic agent

AHEAD Action for Health in Diabetes

AIHW Australian Institute of Health and Welfare

AMPK AMP-activated protein kinase

ARIA Accessibility-Remoteness Index of Australia

ASCVD Atherosclerotic cardiovascular disease

BGL Blood glucose levels

BMI Body mass index

CANVAS Canagliflozin Cardiovascular Assessment Study

CHD Coronary heart disease

CHF congestive heart failure

CI Confidence interval

CKD Chronic kidney disease

CMUS Centre for Medicine Use and Safety

CV Cardiovascular

CVD Cardiovascular disease

CVDL Centre for Victorian Data Linkage

CVOT Cardiovascular outcomes trial

DCSI Diabetes Complications Severity Index

DECLARE–TIMI Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction

DIGAMI Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction

DPP-4 Dipeptidyl peptidase-4

DPP-4I Dipeptidyl peptidase-4 inhibitor

EASD European Association for the Study of Diabetes

eGFR Estimated glomerular filtration rate

EH Eastern Health

ELIXA Evaluation of Lixisenatide in Acute Coronary Syndrome

EMPA-REG OUTCOME Empagliflozin-Removing Excess Glucose

ESRD End stage renal disease

EXAMINE Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care

EXSCEL Exenatide Study of Cardiovascular Event Lowering

FDA Food and Drug Administration

FDC Fixed-dose combination

FPG Fasting plasma glucose

GDM Gestational diabetes mellitus

GIP Glucose-dependent insulinotropic polypeptide

GLD Glucose Lowering Drug

GLP-1 Glucagon-like peptide-1

GLP-1 RA Glucagon-like peptide-1 receptor agonist

HbA_{1C} Glycated haemoglobin A_{1C}

HFRS Hospital Frailty Risk Score

HR Hazard ratio

HUA hospitalisation for unstable angina

IFG Impaired fasting glucose

IGT Impaired glucose tolerance

ILI Intensive lifestyle intervention

IPW Inverse Probability Weights

IQR Interquartile range

K_{ATP} Potassium adenosine triphosphate

LA Lactic acidosis

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

LVEF Left ventricular ejection fraction

MACE major adverse cardiovascular event

MD Mean difference

MEF Medicare Enrolment File

MI Myocardial infarction

NDI National Death Index

NDSS National Diabetes Services Scheme

NL Netherlands

NNH Number needed to harm

NPH Neutral protamine Hagedorn

OR Odds ratio

OGTT Oral glucose tolerance test

PBS Pharmaceutical Benefits Scheme

PI Product Information

PPAR-γ Peroxisome proliferator-activated receptor- γ

PROactive PROspective pioglitAzone Clinical Trial In macroVascular Events

RACGP Royal Australian College of General Practitioners

RAI Rapid acting insulin

RBG Random blood glucose

RCT Randomised controlled trial

REWIND Researching Cardiovascular Events with a Weekly Incretin in Diabetes

RR Relative risk

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

SEIFA Socio-Economic Indexes for Areas

SGLT-2I Sodium-glucose cotransporter-2 inhibitor

SMBG Self-monitoring of blood glucose

SUR Sulfonylurea receptor

SURE Secure Unified Research Environment

SUSTAIN-6 Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes-6

TECOS Trial Evaluating Cardiovascular Outcomes with Sitagliptin

THIN The Health Improvement Network

T1D Type 1 diabetes mellitus

T2D Type 2 diabetes mellitus

T3D Type 3 diabetes mellitus

UKPDS United Kingdom Prospective Diabetes Study

VADT Veterans Affairs Diabetes Trial

VAED Victorian Admitted Episodes Dataset

VIF Variable Inflation Factor

3P-MACE Three-point major adverse cardiovascular event

Background

Before commencing this PhD project, I worked as a community pharmacist, and was struck by both the high prevalence and the destructive impact of type 2 diabetes mellitus (T2D) in my local area. I was aware that the disease was a pandemic and that it was responsible for a considerable amount of morbidity and mortality. I also knew that it disproportionately affected the health of those who were already the most vulnerable people in society, such as older people, those with multiple medical conditions, Aboriginal and Torres Strait Islander people and those at a high level of socioeconomic disadvantage. I also had many questions I wanted to explore; chief among them being "how can I help to prevent people with T2D from being hospitalised or dying as a result of their disease?" Answering this question requires awareness of clinical guidelines, Randomised Controlled Trials (RCTs) and real-world observational studies.

Although it is important to be aware of current best-practice guidelines, it is arguably more important to observe whether such guidelines translate into real-world clinical practice. For example, the T2D clinical guidelines are extremely detailed, and it would be understandable if some clinicians were unaware of some of the finer details of prescribing anti-hyperglycaemic agents (AHAs). Furthermore, the pharmacological treatment of T2D requires a careful weighing of patients' medical and personal characteristics against the risks, benefits, and goals of treatment. For example, the benefits of intensively lowering blood glucose may be outweighed by the risks for some vulnerable individuals, for example, those who are older, frail or have complex comorbidities such as dementia.

It is critical to keep abreast of the constantly evolving literature regarding the safety and efficacy of AHAs, as risks and benefits of different AHAs may take many years to emerge and some medications have more substantial benefits in people with certain comorbidities. An example of this is the recent evidence which suggests that sodium-glucose cotransporter-2 inhibitors (SGLT-2Is), which are relatively new drugs, are particularly effective in people with a history of or at a high risk for heart failure. At present, the benefits, and risks of newer AHAs, such as the SGLT-2Is, in certain vulnerable populations, such as those who have complex health status, are unknown.

Throughout the PhD program, I have been fortunate enough to have access to large, population-based, representative datasets. Through my primary supervisor at Monash University's Centre for Medicine Use and Safety (CMUS), Dr. Jenni Ilomäki, and CMUS director Prof. Simon Bell, I have been granted access to the Pharmaceutical Benefits Scheme (PBS) 10% random sample and the Victorian Admitted Episodes Dataset (VAED) linked to the PBS. I used the former to study patterns and predictors of AHA initiation in Australia and the latter to investigate the cardiac outcomes of SGLT-2Is in frail versus non-frail individuals with T2D.

Through my associate supervisor at Baker Heart and Diabetes Institute, Prof. Dianna Magliano (OAM) and in collaboration with Prof. Jonathan Shaw, I was able to use the National Diabetes Services Scheme dataset (linked to the PBS) to examine rates of additions and switches of AHAs among people with diagnosed T2D who were initiated on AHA monotherapy.

Finally, with the help of Dr. Laura Fanning, I was able to work with a dataset of people with T2D extracted from the Eastern Health (EH) Hospital Network. The purpose of this study was to determine whether age, frailty or dementia predicted the intensity of treatment prescribed for older people with T2D.

Chapter 1: Introduction

Section 1: Type 2 Diabetes Mellitus

1.1.1 The burden of Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2D) is likely to be one of the greatest public health problems of the 21st century [1]. The global prevalence of diabetes is estimated to be 9.3% amongst adults aged 20 to 79 years, and more than 25% amongst older adults aged ≥65 years [2]. T2D accounts for the vast majority (approximately 90%), of all diabetes cases [2]. The global prevalence and incidence of T2D have been rapidly increasing during recent decades, and it is projected that approximately 630 million people will have the T2D by the year 2045 [2]. It is thought that reasons for the increasing prevalence of T2D include rapidly increasing urbanisation, obesogenic environments, aging populations, and improved life expectancies of people with T2D, due to improved management [2].

In Australia, the prevalence of diabetes between 2017-2018 was estimated to be about 5.3% of the adult population, approximately 1.1 million people, [3], and this number is predicted to rise to 1.6 million people by the year 2045 [4]. Diabetes Australia states that there are 100,000 diabetes diagnoses in Australia per year, with between 85-90% of these diagnoses being T2D [5]. The Australian Institute of Health and Welfare (AIHW) estimates that between 2017-2018 approximately 1.1 million hospitalisations were associated with T2D [3]. Despite the high prevalence of T2D, a systematic review of 47 studies from high income countries by Magliano et. al. found that between 2006 and 2014, the incidence of diagnosed diabetes remained stable

in 30% and declined in 36% of included studies [6]. The dramatically increasing prevalence of T2D despite a mostly declining or steady incidence of diabetes is likely indicative of advances in medical treatment which allow people to live with the disease for many years after diagnosis.

Despite medical advances, T2D has a profound impact on life expectancy and quality of life. Systematic reviews have estimated that approximately 32% of people with T2D also have some form of cardiovascular disease (CVD) and that this accounts for approximately half of all deaths in people with T2D [7]. A study from the United Kingdom (UK) found that people with T2D are at a 26% higher risk of mortality (hazard ratio, HR 1.26; [95% confidence interval, CI 1.20; 1.32]) [8]. In Australia, diabetes contributed to around 16,700 deaths, or 10.5% of all deaths, in 2018 [3]. It was the underlying cause of death in 4,700 of these cases and an associated factor in the remaining 12,000 deaths [3]. Type 1 diabetes (T1D) contributed to 5% and the combined effect of T2D and other or unspecified diabetes contributed the other 95% of these deaths [3].

In addition to the very high morbidity and mortality caused by diabetes, there is also a considerable economic burden associated with the disease, with 12% of global healthcare expenditure (USD $760 billion) being allocated to diabetes in 2019 [4, 9]. This figure is projected to increase to USD $845 by the year 2045 [4, 9].

1.1.2 Pathophysiology and complications of diabetes

T2D is characterised by insulin resistance, which results in the impaired ability of the peripheral tissues to uptake and utilise glucose from the bloodstream [10]. The

disease therefore results in high blood glucose levels (hyperglycaemia), which can lead to glucose toxicity. There are also eight well-established physiological defects associated with T2D which are collectively referred to as the “ominous octet” [11]. These include decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic gluconeogenesis, and increased glucagon secretion [11].

T2D is distinct from type 1 diabetes (T1D) in that individuals with T1D are unable to produce sufficient amounts of insulin within the pancreatic beta (β) cells to meet physiological needs, whereas in T2D, the concentrations of insulin in the bloodstream are insufficient to meet cellular glucose demands as a result of cellular insensitivity [10]. Whilst T1D is likely to be detected and diagnosed relatively quickly as a result of prominent symptoms of hyperglycaemia such as polydipsia (extreme thirst), polyurea (frequent urination), fatigue and rapid weight loss, the insidious nature of T2D means that many individuals may remain undiagnosed and untreated for several years before symptoms manifest.

The diagnosis of diabetes may be preceded by prediabetes, which is an intermediate state of hyperglycaemia where glucose levels are higher than normal but have not yet reached the threshold for diabetes diagnosis [12]. It has been estimated that the annual conversion rate of prediabetes to diabetes is between 5% and 10%, although lifestyle interventions in adults during the prediabetes stage can reduce the risk of progression to diabetes by up to 70% [12]. In general, the only pharmacological agent used at the prediabetes stage is metformin as the adverse effects associated

with other agents are generally considered to outweigh the benefits [12]. Definitions of prediabetes vary internationally but the American Diabetes Association (ADA) suggests a prediabetes diagnosis when there is impaired glucose tolerance (140-200 mg/dL measured from an oral glucose tolerance test [OGTT]), impaired fasting glucose (100-125 mg/dL measured from a fasting plasma glucose test) and a glycated haemoglobin A1c (HbA_{1C}) level of 5.7% to 6.4% [12].

Gestational diabetes mellitus (GDM) is diagnosed when initial onset or detection of glucose intolerance occurs during pregnancy, and most women with GDM are asymptomatic [13]. GDM is strongly associated with increased childbearing age, overweight or obesity during pregnancy, personal history of GDM and family history of T2D [13]. GDM typically resolves after childbirth and can be treated with lifestyle modifications such as diet and exercise, or with insulin if the diet and exercise are ineffective [13].

In addition to T1D and T2D, there are hybrid forms which share characteristics of both, for example, slowly evolving, immune mediated diabetes of adults is associated with autoantibodies, similar to T1D but is slow to manifest and β-cell function is typically preserved, which is characteristic of T2D [14]. Another hybrid type is ketosis-prone T2D, which is associated with high blood concentrations of ketones, but individuals with this condition may not require insulin [14]. Other types of diabetes which have different aetiologies to T1D and T2D are rare, and may relate to genetic defects, chromosomal abnormalities, diseases of the exocrine pancreas, endocrine disorders, drugs, chemicals, infections, or immune mediated disease [14].

Diabetes is a risk factor for macrovascular complications including CVDs such as coronary artery disease, heart failure and stroke. In recent decades there has been debate over whether hyperglycaemia is a causative risk factor in the development of atherosclerotic cardiovascular disease (ASCVD) or merely a risk marker brought about by other confounders [15]. However, recent evidence demonstrates that hyperglycaemia *per se* does indeed accelerate and aggravate the process of atherosclerosis [15]. Diabetes also causes microvascular damage including peripheral neuropathy, nephropathy, diabetic retinopathy, impaired immune functioning and reduced inflammatory responses. These pathologies can respectively manifest as neurological pain, chronic renal disease, blindness resulting from diabetic retinopathy, and chronic intractable wounds which may necessitate lower-limb amputation [16].

In recent years, frailty and cognitive decline have been identified as additional complications of diabetes [17]. Frailty is a state of vulnerability brought on by progressive decline across multiple physiological systems, especially as a result of damage to normal cardiopulmonary, neurological, cognitive and neuromuscular functionality [18]. As previously described, diabetes is well known to cause damage to these systems, and this can result in functional impairments, inability to maintain homeostasis, and a loss of physicality, which are hallmarks of frailty [18]. It has also been shown that low glycaemic levels (hypoglycaemia) in older people with diabetes increase the risk of developing frailty, which is thought to be a result of reverse metabolism brought on by malnutrition in this population [18].

A review by de la Monte also found that impaired microcirculation combined with insulin resistance in the brain can cause neurodegeneration which is characteristic of Alzheimer's disease (AD) and that AD could possibly be renamed as type 3 diabetes (T3D) [19]. Despite the fact that T2D may contribute to the progression of AD, it is not thought that T2D causes the disease [11], instead, both T2D and AD are conceptualised as diseases with overlapping pathophysiological features [11]. In both diseases, insulin resistance is fundamentally the result of inflammation, oxidative stress, DNA damage and mitochondrial dysfunction which all contribute to a "degenerative cascade" [11].

1.1.3 Diagnosis of diabetes

There are four tests used in the diagnosis of T2D: Fasting Blood Glucose (FBG), glycated haemoglobin (HbA_{1C}), Random Blood Glucose (RBG) and the OGTT (Figure 1). The FPG test requires eight hours of fasting beforehand, whereas the OGTT measures blood glucose levels (BGLs) two hours after an intake of 75 grams of glucose. The HbA_{1C} test, in contrast, does not require a fasting period but instead indicates glucose control over the previous three months using the concentrations of glycated haemoglobin molecules. According to the World Health Organisation (WHO) Guidelines, a diabetes diagnosis is confirmed in people with symptoms if FBG ≥7.0mmol/L, RBG ≥11.1mmol/L or HbA_{1C} ≥6.5% (44mmol/mol) [14]. Asymptomatic individuals with any test results at these levels will require a repeat test, preferably of the same type, on a separate day, to confirm a diabetes diagnosis [14, 20].

Where an FBG result is between 5.5-6.9mmol/L, an OGTT is performed, which may identify Impaired Fasting Glucose (IFG), (FPG between 6.1-6.9mmol/L, 2-hour blood glucose <7.8mmol/L) or Impaired Glucose Tolerance (IGT), (FBG<7mmol/L, 2-hour blood glucose between 7.8-11.0). Individuals with these diagnoses will require retesting in one year. If the OGTT results are FBG≥7.0mmol/L, 2-hour blood glucose ≥11.1mmol/L then a diabetes diagnosis is confirmed.

HbA_{1C} levels ≥6.5% (48 mmol/ mol) are a better predictor of microvascular disease than the other two tests [21]. One disadvantage of the HbA_{1C} test is its lack of sensitivity and specificity in individuals with haemoglobinopathies, haemolysis, advanced chronic kidney disease or iron deficiencies, or in those who have had a recent blood or iron transfusion [20, 21].

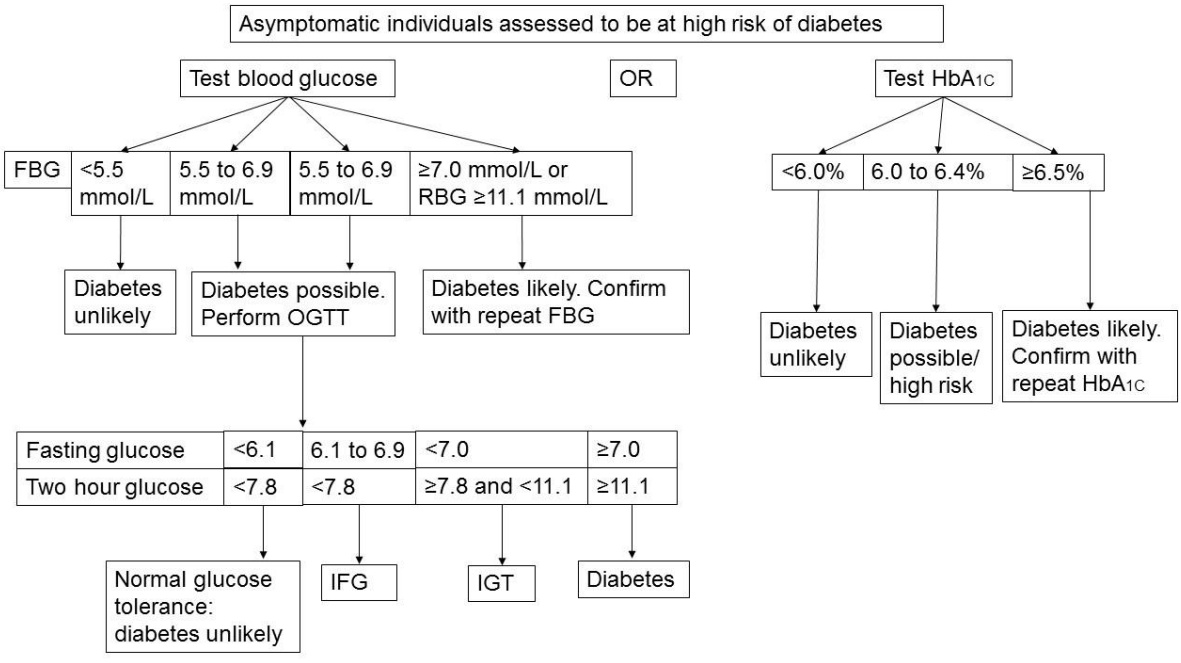

Figure 1: A flowchart for the screening and diagnosis of diabetes. Adapted from [20]

1.1.4 Factors affecting the prognosis of T2D

There is a complex interplay between several factors which can affect the prognosis of people diagnosed with T2D. Some of the most important demographic and clinical characteristics which are most predictive of T2D outcomes are described below.

1.1.4.1 Overweight and obesity

Overweight and obesity are strongly correlated with the development of T2D and it is well-established that obese adolescents who meet guidelines for healthy diet and sufficient exercise are less likely to develop insulin resistance and uncontrolled glycaemic levels [22]. There is also evidence that weight loss can delay development of T2D in people who have prediabetes [22], however there is insufficient evidence to prove that weight loss can prevent the development of vascular complications in individuals with established T2D [23].

The LookAHEAD (Action for Health in Diabetes) trial demonstrated the importance of intensive weight loss for overweight or obese people with T2D [24]. The trial randomised approximately 5,000 overweight or obese individuals (mean Body Mass Index [BMI] of 36kg/m^2), aged between 45 and 75 years, who were receiving routine medical care to receive either an Intensive Lifestyle Intervention (ILI) or routine diabetes support and education [24]. The lifestyle intervention included a combination of calorie-controlled diet plans with <30% of calories being from fat, as well as structured exercise programs available throughout the course of the study. Baseline diabetes duration was 6.8 years on average and blood pressure, lipids and HbA_{1C} were reasonably well controlled at baseline, with 14% of participants having cardiac disease [24]. The primary outcome of the study was time to a major

cardiovascular event [24]. At the conclusion of the trial the ILI group had a 6% weight loss whereas the control group had a weight loss of 3.5 %. The trial was ceased early, with a median follow-up time of 9.6 years, due to futility, as the rate of CVD events was lower than anticipated at 0.7% per year as opposed to the projected 3.1% per year [25]. However, despite this, numerous benefits were noted in the ILI group including improved quality of life, increased insulin sensitivity, glucose control and improved lipid biomarkers, as well as less sleep apnoea, depression, kidney disease, liver fat and urinary incontinence [26]. In addition, there were reductions in financial costs, and improvements in quality-of-life scores. Diabetes was also found to regress in the ILI group [26]. In terms of blood glucose control, the percentage of the ILI group achieving HbA_{1C} <7% increased from 43% to 73%, whereas the percentage of the control group achieving this outcome only increased from 45% to 50% [25].

1.1.4.2 Age and duration of T2D

The prevalence and incidence of the T2D both increases with age before reaching a peak at 85-89 years, and 55-59 years, respectively [27]. Australian statistics also show that T2D hospitalisation rates increase with age, with approximately 87% of T2D hospitalisations between 2017-2018 occurring among individuals aged 55 years and over [3]. There is also an interaction between diabetes duration, age, and microvascular events, such that a 5-year increase in T2D duration has a greater effect on the risk of microvascular events in younger, rather than older individuals [28].

The concept of a “legacy effect” in diabetes refers to the observation that extended periods of hyperglycaemia are associated with vascular events which occur many years later, as though there exists a so-called “metabolic memory” [29]. Zoungas et al. have shown that every 5-year increase in duration of T2D is associated with a higher risk of macrovascular (Hazard ratio [HR] 1.13; 95%CI [1.08—1.17]) and microvascular (HR 1.28; 95%CI [1.23—1.33]) complications as well as all-cause death (HR 1.15; 95%CI [1.10—1.20]) [28].

T2D was previously referred to as “mature onset diabetes,” however, this is no longer considered accurate terminology as T2D has become more prevalent in younger people in recent years [30]. In the UK, the prevalence of diabetes among children and adolescents rose by almost tenfold (from 0.21/100,000 to 1.9/100,000) between the years 1998 and 2005 [30, 31]. This is particularly concerning as earlier onset T2D is characterised by a severe complication trajectory, more aggressive disease and a heightened risk of psychological morbidity and vascular complications [30].

1.1.4.3 Sex

Between 2017-2018 the prevalence of T2D in Australia was slightly higher among males (6.1%) than females (4.6%) [3]. The rates of T2D-related hospitalisations were approximately 40% higher for males than females during the same period [3]. Data from cohort studies have shown that women with T2D have three times the risk of cardiovascular mortality compared to women without T2D, whereas cardiovascular death was only about 1.5 times as likely in men with T2D, compared to those without it [32]. Systematic reviews have found that women with diabetes have a 40%

elevated risk of incident coronary heart disease (CHD) and are 30% more likely to experience a stroke compared to men with diabetes [33].

Women with T2D are also more likely than men with T2D to be obese or to experience psychological distress [34]. Rates of nonadherence to CVD therapies, failure of glucose lowering therapy and hypoglycaemia associated with insulin therapy are also more likely in women with T2D, compared to men with T2D [34].

1.1.4.4 Sociodemographic factors

There is clear evidence that the prevalence of T2D in Australia decreases with increasing affluence [35]. In Australia, the prevalence of T2D between 2017-2018 was about twice as high amongst people living in the lowest socioeconomic areas (7.0%) compared to the highest (3.3%) [3]. During the same period in Australia, rates of T2D-related hospitalisation were approximately double among people with T2D living in the lowest compared to the highest levels of socioeconomic advantage [3]. A recent systematic review including studies from around the world found evidence that socioeconomic disadvantage also increases the risk of complications such as retinopathy (9 of 14 studies) and cardiopathy (8 of 9 studies) in people with T2D [36].

Indigenous communities also bear a disproportionately higher burden of T2D, and this is particularly prominent in Australia's Aboriginal and Torres Strait Islander population, in which individuals are eight times as likely to develop diabetes than Caucasian Australian individuals [37]. Aboriginal and Torres Strait Islander persons with T2D also have approximately 6.6 times the rate of end-stage renal disease (ESRD) due to T2D compared to other Australians [35].

In Australia, the prevalence of T2D between 2017-2018 was relatively similar in outer regional and remote areas (6.0%) compared to major cities (4.8%), however, hospitalisation rates for T2D were 2.5 times as great in remote and very remote areas compared to major cities [3]. Higher T2D-related hospitalisation rates in rural and remote areas are hypothesised to be at least partially attributable to difficulties in the long-term management of T2D [38]. Such issues may relate to the accessibility of healthcare centres [38].

1.1.4.5 Tobacco smoking

Tobacco smoking has been shown in a systematic review by Maddatu et. al. to be a likely factor in the development of hyperglycaemia and T2D [39]. There is also clear evidence that smoking further compounds the already significant effect of T2D on the risks of all-cause mortality and cardiovascular death [40]. A meta-analysis estimated the pooled adjusted relative risk [RR] associated with smoking in people with T2D to be 1.55 (95%CI [1.46—1.64]) for total mortality and 1.49 (95%CI [1.29—1.71]) for cardiovascular mortality, compared to non-smokers with T2D [41].

1.1.4.6 Medications

AHAs by definition, work to lower physiological BGLs and will be discussed in detail in Chapter 1, Section 2 of this thesis. However, there are numerous other categories of medications which affect BGLs and alter the prognosis of T2D. Many medications which are unrelated to the treatment of T2D can raise BGLs. Examples include corticosteroids, and antipsychotics. Hyperglycaemia is a predictable adverse event caused by long-term oral glucocorticoid therapy and is associated with a 36% increase in odds of developing new-onset diabetes [42]. The prevalence of post-

prandial hyperglycaemia is approximately 42% in people without diabetes taking oral glucocorticoids [43]. It is uncertain whether inhaled corticosteroids used for the treatment of asthma or COPD can exacerbate glycaemic control [43].

Atypical antipsychotics such as olanzapine, lurasidone, ziprasidone and risperidone are more likely to increase BGLs than typical antipsychotics, although a recent network meta-analysis reported that only olanzapine (mean difference [MD] 3.95; 95%CI [0.14-7.76]) did this to a significant extent, compared to placebo [44]. It was also reported that olanzapine causes greater increases in BGLs compared to other commonly used atypical antipsychotics [44].

A principal concern in the management of T2D is the control of modifiable cardiovascular risk factors. This can be achieved pharmacologically through a combination of anti-hypertensive and lipid-lowering medications. Overall, such medications confer far greater benefits than risks for people with T2D, in terms of cardiovascular outcomes and mortality, however a small number of them can elevate BGLs. Thiazide diuretics and β-blockers used for hypertension have been shown to raise BGLs, however it is unclear whether this drug-induced diabetic state is associated with the same deleterious effects on vascular outcomes as “traditional” T2D [45]. Statins are a class of lipid-lowering medications which have been shown to precipitate T2D [46], although they do not worsen BGLs after T2D has been diagnosed [47].

1.1.4.7 Multimorbidity

The presence of comorbid medical conditions in people with T2D is known to increase mortality risk [48]. A longitudinal cohort study among individuals from the UK found that the combination of both coronary heart disease and heart failure in addition to T2D had the largest effect on mortality, (HR 4.37; 95%CI [3.59–5.32]), compared to individuals with T2D without comorbidities [48]. It was also found that the risk of all-cause mortality in people with T2D increased with increasing comorbidity numbers [48]. One (HR 1.20; 95%CI [0.91–1.56]), two (HR 1.75; 95%CI [1.35–2.27]), three (HR 2.17; 95%CI [1.67–2.81]), and four or more additional conditions, (HR 3.14; 95%CI [2.43–4.03]), respectively, increased the risk of mortality in people with T2D, compared to people with T2D without comorbidities [48].

An Australian cross-sectional study found that more than 90% of people with T2D were living with multimorbidity [48]. It also noted that the three most prevalent co-occurring conditions which were related to T2D (concordant conditions) were hypertension (61.4%), coronary heart disease (17.1%) and chronic kidney disease (8.5%) [48]. However, there was no relation between the number of comorbidities and HbA_{1C} levels [48].

1.1.5 Glycaemic targets

Australian and international guidelines recommend HbA_{1c} ≤7.0% should be set as a general target for people with T2D [49-52]. Nevertheless, numerous RCTs which shall be described later in this section have indicated that the benefits of more intensive treatment targets may be outweighed by the risks, particularly for HbA_{1C}

levels <6.0% [53]. These studies have led to the notion of setting individualised glycaemic targets for people with T2D who are unlikely to benefit from stringent glycaemic control. Australian general practice guidelines as well as ADA guidelines advise that glycaemic targets should be made less stringent, (HbA_{1C} <8.0%) for people with shorter life expectancies, established vascular complications, longstanding T2D duration, risk factors for hypoglycaemia and important comorbidities [20, 50]. People who are non-adherent, have poor self-care capacity or lack resources and support systems may also benefit from less intensive glycaemic targets, although such factors may be modifiable [20, 50].

Four landmark RCTs which investigated the effects of various T2D treatment strategies on vascular outcomes were the United Kingdom Prospective Diabetes Study (UKPDS) [54], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [53], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [55] and Veterans Affairs Diabetes Trial (VADT) [55]. These studies aimed to establish the effects of different AHAs available at the time and different treatment intensities on microvascular and macrovascular outcomes in people with T2D.

The UKPDS determined that intensive metformin therapy was a suitable treatment for a subgroup of overweight individuals with recently diagnosed T2D, as it reduced the incidence of cardiovascular outcomes compared to people given diet-only or intensive treatment with either sulfonylurea or insulin [54]. It also found that although the more intensively treated group, compared to standard care group did not have a lower risk of macrovascular events, a 1% reduction in HbA_{1C} resulted in a 25%

reduction in risk of microvascular outcomes [56]. The UKPDS prompted the evolution of the previously described concept of a “legacy effect.” Since this study included newly diagnosed individuals with T2D, the concept of a positive legacy effect was also proposed and the importance of early and sustained blood glucose control was emphasised [29]. Subsequent analyses of the UKPDS data showed a linear relationship between HbA_{1C} levels and micro and macro vascular complications, which led to the design of several other studies which aimed to assess the effects of more intensive HbA_{1C} control [56].

In contrast to the UKPDS, the ACCORD study, estimated a statistically significant 22% increased risk of mortality amongst those in the intensive treatment arm, which led to discontinuation of the study after 3.5 years [53]. The baseline mean HbA_{1C} in ACCORD was 8.1% and patients were assigned to receive either standard therapy (targeting HbA_{1C} of 7.0 to 7.9%) or intensive therapy (targeting HbA_{1C}<6.0%) [53]. The 10,251 individuals participating in ACCORD had a mean age of 62.2 years, which was notably older that in the UKPDS (53 years) and 35% had experienced a prior cardiovascular event [53]. Those receiving intensive treatment did not have significantly reduced risks of cardiovascular events, compared to the control group, but had greater risks of mortality, hypoglycaemia requiring assistance and >10kg weight gain [53]. The fact that participants in the ACCORD study had a higher mean age and a greater burden of CVD than those in the UKPDS, raised the prospect that the harms of intensive glycaemic control may be greater for older and more vulnerable individuals. An important concept to arise from the ACCORD study was the “J curve”, (Figure 2), which illustrates that cardiovascular outcome risk generally

decreases with reductions in glycaemic levels, but then increases again when targets become too stringent.

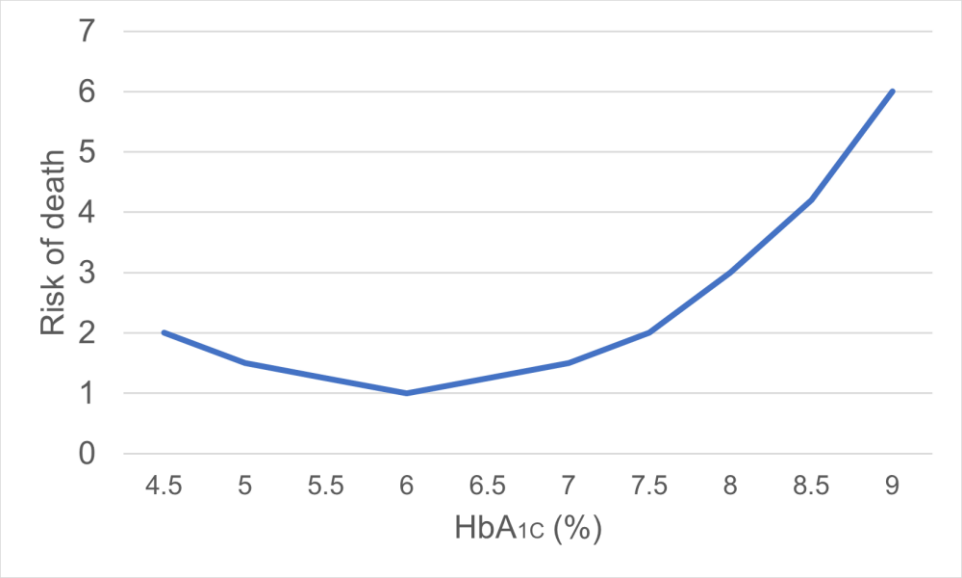

Figure 2: An illustration of the concept of a “J curve”. Glycaemic targets below a certain threshold are associated with increased risks of negative cardiovascular outcomes and death. Adapted from [57].

The ADVANCE study investigated the macro and microvascular risks of intensive therapy, compared to standard therapy utilising a less aggressive target (HbA_{1C}<6.5%) than the ACCORD study [55]. In ADVANCE, 11,140 people with T2D were randomised and then followed-up for a median of 5 years, at which point the mean HbA_{1C} was lower in the intervention (6.5%), compared to the control group (7.3%) [55]. It was found that that the risks of major macro and microvascular events were both significantly reduced in the intervention group, compared to the control group, (HR 0.90; 95%CI [0.82—0.98]) and (HR 0.86; 95%CI [0.77—0.97]), respectively [55]. Severe hypoglycaemia, however, was still more common in the more intensively-treated group (HR 1.86; 95%CI, [1.42—2.40]) [55].

The VADT was designed to investigate the effect of intensive glucose control, versus standard treatment on time to a major adverse cardiovascular event (MACE) among 1,791 military veterans, mean age 60.4years, 40% with a prior cardiovascular event and mean diabetes duration of 11.5 years [58]. In this trial, MACE was defined as a composite of myocardial infarction (MI), stroke, cardiovascular death, congestive heart failure (CHF), surgery for vascular disease, inoperable coronary disease, or amputation for ischemic gangrene [58]. After 5.6 years of follow-up, it was found that intensive treatment did not significantly affect time to MACE occurrence (HR 0.88; 95%CI [0.74—1.05]), nor did it affect the risk of all-cause mortality (HR 1.07; 95%CI [0.81—1.42]), [58].

The conclusion from reviewing the aforementioned studies is that whilst intensive glucose control (HbA_{1C}< 6.0%) is effective in preventing macrovascular events such as nephropathy, there is little convincing evidence that it protects against macrovascular outcomes, particularly in the short to medium term. On the contrary, it is evident that the increased risk of hypoglycaemia and death, particularly among older people or those with prior cardiovascular events, makes intensive control a poor strategy in general.

Section 2: Pharmacotherapies for T2D

1.2.1 Biguanides: Metformin

Currently, metformin is the only AHA within the biguanide class in Australia. Metformin is an AMP-activated protein kinase (AMPK) activator which inhibits hepatic gluconeogenesis and enhances insulin mediated glucose uptake in peripheral tissues [59]. Metformin also has beneficial effects on lipid profiles and both endothelial and vascular function, although the details of these mechanism of action are largely still unclear [60]. Metformin has many advantages over other AHAs as it is inexpensive, exhibits an excellent cardiovascular safety profile and is taken orally. It also does not cause weight gain and may cause weight loss through appetite suppression [61]. Metformin is generally well tolerated, with its principal adverse drug reactions being gastrointestinal, including abdominal discomfort, bloating and diarrhoea [62]. It reduces HbA_{1C} by approximately 1.5% percentage points, compared to placebo [63] and can result in sustained weight loss of up to 2.5kg, compared to lifestyle interventions alone [64]. Standard doses of metformin (>1500mg per day) are known to cause vitamin B_{12} deficiency, but this can generally be managed by taking a multivitamin [65].

Recent systematic reviews have demonstrated that metformin is associated with a lower incidence of dementia (HR 0.76; 95%CI [0.39—0.88]) [66]. Cognitive impairment was also found to be less common in people taking metformin for diabetes (odds ratio [OR]0.55; 95%CI [0.38 to 0.78]), however there is insufficient evidence for it to be used in people at risk of developing dementia who do not have T2D [66]. Metformin is cleared by the renal system and there have been historical

concerns about its propensity to cause lactic acidosis (LA), especially at high concentrations, in people with renal impairment [62]. A 2014 systematic review found that metformin is not associated with a substantial increase in lactate concentrations in patients with mild to moderate chronic kidney disease (CKD), (estimated glomerular filtration rate [eGFR] between 30-60 mL/min per 1.73 m^2) [67]. This review also noted that LA is exceedingly rare in metformin users with T2D (3-10 events per 100 000 person-years) and that rates of LA among metformin users are not discernibly different from the background rates in people with diabetes who do not use metformin [67]. As of 2016, the US Food and Drug Administration (FDA) removed a black box warning from the metformin Product Information (PI) and declared that it is safe to use in individuals with eGFR ≥30 mL/min/1.73 m^2 [68]. Similar concerns about a possible link between metformin and LA in people with heart failure existed until the early 2000s, but systematic reviews have found no evidence for the veracity of this association [69].

1.2.2 Insulin secretagogues: Sulfonylureas

Sulfonylureas are the oldest and most widely prescribed class of AHAs worldwide [60]. Their mechanism of action results in release of insulin from pancreatic β-cells. The sulfonylurea receptor (SUR) of the potassium adenosine triphosphate (K_{ATP}) channel associated with pancreatic β-cells is the primary target of sulfonylureas [70]. Binding of sulfonylureas to the SUR binding site closes the K_{ATP} channels, resulting in depolarisation of the β-cell membranes, followed by the opening of voltage-dependent calcium channels, which triggers calcium cation (Ca^{2+}) influx and exocytosis of insulin granules [70].

Whilst the first-generation sulfonylureas, tolbutamide and chlorpropamide, are no longer used, the second generation (glipizide, glibenclamide and gliclazide) and third generation (glimepiride) sulfonylureas continue to be mainstays of T2D therapy [71]. Advantages of sulfonylureas include their low cost, oral dose form and their potent effects on short-term blood glucose control (reduction in HbA_{1C} by 1-2 percentage points) [72]. Individuals with severe chronic renal failure can be prescribed either gliclazide or glipizide at reduced doses, however glibenclamide and glimepiride are contraindicated due to significant renal excretion and active metabolites, respectively [73]. The most important disadvantages of sulfonylureas are their high tendency to induce weight gain (mean weight gain of 5.3kg over 6 years) [54] and mild (RR 2.95; 95%CI [2.13—4.07]) or severe hypoglycaemia (RR 5.64; 95%CI [1.22—26.00]) [74].

1.2.3 Thiazolidinediones

The two thiazolidinediones available in Australia and internationally are rosiglitazone and pioglitazone, both of which are insulin sensitisers. Thiazolidinediones activate Peroxisome Proliferator-Activated Receptors-γ (PPAR-γs), which results in the expression of genes involved in carbohydrate, lipid and protein metabolism [75]. PPAR-γ activation is also associated with adipocyte differentiation, increased insulin sensitivity, oxidative stress prevention and modulation of immune responses implicated in the pathogenesis of insulin resistance [75]. These medications have the advantages of being available as oral dose forms, conferring benefits in atherosclerosis and having a low risk of causing hypoglycaemia [76]. This class can, however, cause weight gain, reductions in bone mineral density [77] and fluid retention which can lead to heart failure [76]. Cardiovascular outcomes of thiazolidinediones will be discussed further in Chapter 1, Section 2.9.3 of this thesis.

Early analyses of pioglitazone clinical trials data [78] led to speculation that the medication may increase the risk of bladder neoplasms, but a more recent analysis involving 6 years of follow-up has determined that it does not [79].

1.2.4 Alpha Glucosidase inhibitors: Acarbose

Acarbose delays the breakdown of complex carbohydrates into monosaccharides through the competitive, reversible inhibition of intestinal alpha-glucosidases [80]. Because of the delay in postprandial glucose levels, acarbose attenuates the subsequent release of insulin, thereby reducing triglyceride uptake into peripheral tissues [80]. Acarbose can reduce HbA_{1C} levels by approximately 0.1-1.0 percentage units (%-units) and is especially useful where postprandial hyperglycaemia is problematic [81]. It is also unlikely to cause weight gain or hypoglycaemia [81]. Rare cases of elevated serum transaminase levels have been reported but gastrointestinal problems appear intolerable for many people [81]. As acarbose is dispensed for less than 1% of all people dispensed AHAs in Australia [82]. It will not be discussed further in this thesis.

1.2.5 Incretin enhancers: Dipeptidyl Peptidase-4 Inhibitors (DPP-4Is)

The incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) enhance insulin secretion in response to elevated BGL, and therefore protect against postprandial hyperglycaemia [70]. In people without diabetes, incretins cause approximately 50-70% of post-prandial insulin secretion, but this reduces to 20-35% in people with T2D, due to incretin resistance [83]. It has been found that DPP-4Is, also known as gliptins, inhibit the enzyme responsible for

incretin degradation (dipeptidyl peptidase-4) and thus, are classified as incretin enhancers [70].

DPP-4Is available in Australia include sitagliptin, saxagliptin, vidagliptin, linagliptin, and alogliptin which also exist in Fixed Dose Combination (FDC) products in combination with other AHAs, most commonly metformin. DPP-4Is do not increase the risk of hypoglycaemia, compared to placebo, do not cause weight changes and are generally able to be used in people with renal impairment at reduced doses [61]. The most frequently reported adverse events associated with this class include nasopharyngitis, upper respiratory tract infections and headaches [61].

1.2.6 Incretin mimetics: Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

GLP-1 RAs, like DPP-4Is, activate the incretin pathway, but do so by mimicking the actions of GLP-1 and potentiating GLP-1 signalling on pancreatic β-cells. This class of AHAs partially overcome the incretin resistance which occurs in T2D [83] by augmenting this signalling pathway. GLP-1RAs are known to decrease glucagon secretion, while enhancing insulin secretion in response to hyperglycaemia [84]. They also promote weight loss as they slow gastric emptying and improve satiety, hence they are currently being trialled as weight loss drugs in people without T2D [84, 85]. Disadvantages of this class of AHAs include that they must be injected subcutaneously and can cause gastrointestinal disturbances such as nausea, vomiting and diarrhoea. Exenatide is contraindicated when eGFR< 30 mL/min per 1.73 m^2, whilst the other GLP-1 RAs are to be used only under the close supervision of a physician if prescribed for people with an eGFR< 30 mL/min per 1.73 m^2 [86].

Currently dulaglutide, exenatide twice daily (BD), exenatide once weekly (QW), liraglutide, lixisenatide and semaglutide are available in Australia, however, during the periods of the studies described in Chapters 2 to 5 of this thesis, only exenatide BD was subsidised by the PBS.

1.2.7 Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2Is)

The mechanism of SGLT-2Is involves the inhibition of renal sodium glucose-2 cotransporters in the renal proximal convoluted tubule, which results in increased excretion of glucose and glycosuria [87]. SGLT-2Is are a relatively new class of AHA which have been shown to have numerous benefits on heart failure hospitalisations, cardiovascular mortality, and renal disease, especially for individuals with T2D and CVD [87, 88]. These will be discussed in more detail in section 2.9.6. This class has several benefits including reductions in blood pressure, HbA_{1C} (by 0.5%-units) and body weight [61]. The reduction in body weight is thought to be mainly attributable to osmotic diuresis during the first few weeks of use, however, longer term weight loss results from lipolysis due to the excretion of excess blood glucose [89]. SGLT-2Is are also very unlikely to cause hypoglycaemia because of their insulin-independent mechanism and may be used during the later stages of T2D after pancreatic β-cell depletion or exhaustion [61].

SGLT-2Is are also considered to be reno-protective. Dapagliflozin was found in the DECLARE-TIMI 58 trial to reduce the risk of a renal composite outcome (≥40% decrease in eGFR to <60 ml per minute per 1.73 m^2, new end-stage renal disease, or death from renal or cardiovascular causes) by 24% (HR 0.76; 95%CI [0.67—0.87]) [90]. The CANVAS study also found that canagliflozin is likely to have

positive effects on the progression of albuminuria (HR 0.73; 95% CI [0.67—0.79]) and the composite outcome of sustained ≥40% reduction in eGFR, need of renal-replacement therapy or renal death, (HR 0.60; 95% CI, [0.47—0.77]) [91]. However, based on the prespecified hypothesis testing sequence, the authors of CANVAS cautioned that these results were not viewed as statistically significant [91]. The CANVAS study also identified that canagliflozin's adverse event profile includes a higher risk of amputations (HR 1.97; 95% CI, [1.41—2.75]), most frequently of the toe or metatarsal, although this has not been confirmed in other RCTs [91, 92].

Common adverse events associated with SGLT-2Is are genitourinary infections, particularly urinary tract infections (UTIs) and genital mycoses [61]. Rarely, SGLT-2Is can cause euglycaemic diabetic ketoacidosis (EDKA), which is a medical emergency manifests with symptoms of abdominal discomfort, fatigue, nausea and vomiting [61]. Despite their long-term reno- protective effects, there have been concerns about acute kidney injury (AKI) in the first few months after SGLT-2I initiations [93]. A recent cohort study, however, has shown that these concerns may be unwarranted, and that SGLT-2Is actually reduce the 90-day risk of AKI hospitalisations compared to DPP-4Is, weighted risk ratio 0.79 (95%CI [0.64—0.98]) [94].

1.2.8 Insulin

Insulin is first-line and life-saving for people with T1D, however, the use exogenous insulin in people with T2D tends to be reserved until other treatment options have failed or hyperglycaemia becomes uncontrolled [20]. As T2D progresses, insulin sensitivity and physiological insulin secretion can reduce to the point where additional insulin is required [95].

Although insulin potently reduces HbA_{1C} and blood glucose levels, its use as a medication for T2D is associated with numerous challenges [95], many of which result from the subcutaneous route of administration [96]. Non-adherence can result from numerous psychosocial and cultural factors as well as fears of hypoglycaemia, perceived impacts on normal daily activities and the cumbersome nature of needing frequent injections [96]. The prospect of regular injections and self-monitoring of blood glucose (SMBG) is also overwhelming for many people, in part because of a fear of the pain associated with injections [97]. Adverse events from insulin include pronounced weight gain, hypoglycaemia, iatrogenic hyperinsulinaemia [98] as well as lipoatrophy or lipodystrophy if injection sites are not rotated [97], which all add to the burden of using this medication.

When first- and/ or second-line treatment options have been trialled but have not adequately resolved hyperglycaemia, insulin can be added to the AHA regimen. Insulin may also be indicated when the disease progresses to the point where previously controlled T2D becomes uncontrolled (HbA_{1C}> 9.0%) [50]. Basal insulins such as insulin glargine or insulin detemir are used as a starting point to control fasting glucose, rather than neutral protamine Hagedorn (NPH) [95]. This is because of basal insulins' lower tendency to cause hypoglycaemia, due to lower blood-insulin peaks and their slow-release profile, which results in a longer duration of action [95].

The intensification of basal insulin generally involves one of two options. The first is addition of a prandial rapid acting insulin (RAI) or biphasic (mixed) insulin to existing basal insulin therapy. RAIs such as insulin lispro, aspart and glulisine, may be taken at around the time of the most carbohydrate heavy meal of the day (basal plus), and

then also added, if required, to another one or two means daily (basal-bolus) [95]. Alternatively, mixed insulins can be added to a basal regimen for individuals who struggle with basal-bolus regimens. Mixed insulins generally contain a rapid-acting insulin combined with a neutral or intermediate acting insulin and therefore require fewer injections than basal-bolus; however, they are also less flexible and result in poorer glycaemic control, more hypoglycaemia and more weight gain than basal bolus regimens [95]. Another option when intensifying basal insulin is for a GLP-1 RA to be prescribed [95]. Although potentially more expensive, the addition of a GLP-1 RA has been shown to be preferable to adding prandial RAIs or mixed insulins, as it causes less weight gain, less hypoglycaemia and has equal or superior efficacy, despite reduced regimen complexity [99].

1.2.9 Cardiovascular safety of anti-hyperglycaemic agents

1.2.9.1 Cardiovascular safety of metformin

Metformin may reduce the risk of cardiovascular events and death, particularly after 10 years of use [100]. The UKPDS 34 study provided important evidence for the advantages of metformin use in overweight individuals with T2D [54]. This RCT randomised 1,704 overweight individuals with newly diagnosed T2D, without hyperglycaemic symptoms, into one of three groups [54]. These groups were: diet alone, (n=411), intensive therapy (target FPG of <6 mmol/L) with metformin, (n=342), or intensive therapy using either sulfonylureas or insulin (n=951) [54]. The mean age of participants was 53 years, the median duration of follow-up was 10.7 years and the primary outcomes were aggregates of any diabetes related clinical endpoint, diabetes related death and all-cause mortality [54]. Compared to the diet-only group,

metformin recipients had significant risk reductions for any diabetes related end point (RR 0.68, 95%CI [0.53—0.87]), diabetes related death (RR 0.58; 95%CI [0.37—0.91]) and all-cause mortality (RR 0.64; 95%CI [0.45—0.91]) [54].

A meta-analysis published in 2017 analysed 13 trials, to determine the impact of metformin on cardiovascular outcomes [101]. Trials analysed included 2,079 individuals with T2D who were either allocated metformin or a comparator treatment of diet, lifestyle or placebo [101]. Results of this analysis indicate that metformin does not convincingly protect against outcomes such as all-cause mortality (RR 0.96; 95%CI [0.84—1.09]), cardiovascular death (RR 0.97; 95%CI [0.80—1.16]), myocardial infarction (RR 0.89 95%CI [0.75—1.06]), stroke (RR 1.04 95%CI 0.73—1.48) or peripheral vascular disease (RR 0.81; 95%CI [0.50—1.31]) [101]. The review acknowledges that effect sizes were based on relatively low numbers of outcomes (416 MIs or ischaemic heart disease [IHD] events from seven studies and 111 strokes from four studies), and also identifies that participants were predominantly white, 65 years of age or less, overweight or obese and did not have good glycaemic control [101].

1.2.9.2 Cardiovascular safety of sulfonylureas

The literature concerning the cardiovascular safety of sulfonylureas, compared to metformin is mixed and, at times, contradictory. A Cochrane Review comparing metformin to sulfonylurea monotherapy concluded that currently used sulfonylureas may decrease the risk of nonfatal macrovascular events (RR 0.67; 95%CI [0.48—0.93]), compared with metformin, but that more trials are needed to confirm this, due to variations between studies in how this outcome was defined [74]. This

review also noted, however, that sulfonylurea compared to metformin monotherapy did not reduce the risk of all-cause (RR 0.98, 95%CI [0.61—1.58]) or cardiovascular mortality (RR 1.47, 95% CI 0.54 to 4.01),

In contrast, observational studies have shown that initiation of T2D treatment with sulfonylureas, compared to metformin is associated with greater risks of ischaemic stroke, cardiovascular death, and all-cause mortality [102]. A retrospective cohort study by Roumie et. al. reported that individuals with diabetes and reduced kidney function had a lower incidence of MACE after a median follow-up time of 1.1 years if they were newly initiated on metformin compared to a sulfonylurea (23 versus 29.2 events per 1000 person-years) [103]. The cause-specific adjusted HR of MACE for metformin was 0.80 (95%CI [0.75—0.86]) compared with sulfonylureas [103].

1.2.9.3 Cardiovascular safety of thiazolidinediones

There has been significant controversy over the cardiovascular safety of thiazolidinediones [104-107] since a meta-analysis in 2007 flagged an increased risk of MI (OR 1.43; 95%CI [1.03—1.98]), as well as a statistically borderline increase in the risk of death from cardiovascular causes, compared to placebo and standard care (OR 1.64; 95%CI [0.98—2.74]) [106]. A more recent systematic review and meta-analysis using individual patient level data from RCTs confirmed that rosiglitazone was associated with 33% (OR 1.33; 95%CI [1.09—1.61]) increased odds of a combined outcome of MI, heart failure, cardiovascular related death, and non-cardiovascular related death, compared to controls [108]. A teleo-analysis of thiazolidinediones' effects on heart failure has also estimated that the number needed to harm (NNH) is approximately 50 over a 2.2-year period [109]. The

development of heart failure is thought to be a class effect of thiazolidinediones which is linked to plasma volume expansion from an increase in sodium reabsorption in the collecting tubules, rather than from direct cardiac damage [109].

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study investigated whether pioglitazone reduced macrovascular complications compared to placebo when added to standard care in people with T2D and evidence of macrovascular disease [110]. The study randomised 5,238 individuals. PROactive found that pioglitazone, after a mean duration of 34.5 months, did not significantly reduce the risk of the primary outcome (HR 0.90; 95%CI [0.80—1.02]), defined as either all-cause mortality, non-fatal MI or stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, an above-ankle amputation [110]. However, it did reduce the risk of the secondary outcome (HR 0.84; 95%CI; [0.72—0.98]), which was a composite of all-cause mortality, non-fatal MI and stroke [110, 111].

Another RCT by Giles et al. compared pioglitazone's association with hospitalisation for heart failure (HHF) or death from heart failure among people with T2D, systolic dysfunction and New York Heart Association Functional Class II/III Heart Failure [112]. This study found that pioglitazone, compared to glibenclamide (±insulin) controls, was associated with a higher probability of the primary outcome, which was a composite of cardiovascular mortality or hospitalisation or emergency room admission for heart failure, (pioglitazone [13%] versus glibenclamide (±insulin) [8%], [p= .024]) [112]. This result was thought to be largely driven by a higher probability of HHF (9.9% versus 4.7%, no p-value provided). Unexpectedly, it was also shown that pioglitazone preserved, rather than worsened left ventricular ejection fraction (LVEF),

compared to glibenclamide (±insulin), LVEF (%) (3.6 [10.20] and 2.5 [9.86], respectively; P = .413) [112], although the duration of the study was only 6 months.

1.2.9.4 Cardiovascular safety of DPP-4Is

Following the findings of increased MI risk associated with rosiglitazone in 2007, the US FDA mandated that all AHAs be tested for cardiovascular safety in cardiovascular outcomes trials (CVOTs) [113]. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial examined 16,492 patients with T2D with a history of or a high risk of cardiovascular events who were randomly assigned to receive either saxagliptin or placebo [114]. The primary end point was 3 Point Major Adverse Cardiovascular Event (3P-MACE) defined as a composite of cardiovascular death, nonfatal MI, or nonfatal ischaemic stroke [114]. Saxagliptin did not reduce the risk of the primary outcome (HR 1.00; 95%CI [0.89-1.12]), compared to placebo [114], although it was associated with a time-dependent increase in risk of HHF, with the risk reducing over time from one year of follow-up (HR 1.46; 95%CI [1.15–1.88]) [115] to two years (HR 1.27; 95% CI [1.07 to 1.51]) [114]. History of heart failure also modified the effect of saxagliptin on HHF. In the stratum of individuals without a history of heart failure, saxagliptin increased the risk of HHF (HR 1.32; 95%CI [1.04–1.66]), whereas in the stratum with heart failure history it did not affect the relative risk of HHF (HR 1.21; [0.93–1.58]). [115].

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial included 5,380 people with MI or hospitalisation for unstable angina (HUA) within the previous 90 days, who were followed up for up to 40 months

and monitored for their development of a primary composite outcome of 3P-MACE [116]. Alogliptin was noninferior to placebo with respect to the primary outcome (HR 0.96; upper boundary of the one-sided repeated confidence interval 1.16). Similarly, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomised 14,671 individuals to receive either sitagliptin or placebo with the primary outcome being 3P-MACE or HUA [117]. After a median follow-up time of 3.0 years, sitagliptin was also found to be noninferior to placebo with respect to the primary outcome (HR 0.98; 95%CI [0.88—1.09]) and with respect to HHF (HR 1.00; 95%CI [0.83—1.20]). Taken together, the results of the CVOTs indicate that DPP-4Is, as a class, do not cause an increased risk of adverse cardiovascular outcomes, although there is evidence that saxagliptin may confer a greater relative risk of HHF, particularly within the first year of use and in people without a history of heart failure.

1.2.9.5 Cardiovascular safety of GLP-1RAs

Some, but not all, GLP-1RAs have been shown to be superior to placebo in reducing cardiovascular outcomes in people with T2D. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial randomised 6,068 individuals ≥30 years, with a history of ACS within the previous 180 days, into a lixisenatide or placebo group [84]. The primary outcome of this trial was either 3P-MACE or HUA and the median follow-up time was 25 months [84]. Lixisenatide was not found to significantly affect the risk of the primary outcome (HR 1.02; 95%CI [0.89—1.17]), compared to usual care plus placebo. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) examined the cardiovascular safety of once weekly exenatide among 14,752 individuals, of whom 73.1% had CVD over a median follow-up period of 3.2 years [118]. It was found that in people with T2D, with or without CVD, once weekly

exenatide was non-inferior, but not superior to standard care plus placebo with respect to MACE (HR 0.91; 95%CI [0.83 to 1.00]) [118].

In contrast, numerous GLP-1RAs have shown substantial protective effects against MACE. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which enrolled 9340 individuals, examined the primary outcome of 3P-MACE [119]. The study had a follow-up period of 3.8 years and only included individuals aged ≥50 years with a cardiovascular risk factor or prior cardiovascular episode [119]. Results indicated that liraglutide significantly reduced the risk of the primary outcome (HR 0.87; 95%CI [0.78 to 0.97]), cardiovascular death (HR 0.78; 95% CI, [0.66 to 0.93]) and all-cause mortality (HR 0.85; 95%CI; [0.74 to 0.97]), compared to placebo [119].

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes-6 (SUSTAIN 6) CVOT included 2,735 individuals with a median follow-up time of 2.1 years [120]. Semaglutide was found to have a significant positive effect on the primary outcome of MACE (HR 0.74; 95%CI; [0.58 to 0.95]) and a borderline statistically significant effect on nonfatal stroke (HR 0.61; 95%CI; [0.38 to 0.99]) [120]. Post-hoc analyses confirmed that these effects on MACE applied, regardless of gender, age, or baseline cardiovascular risk profile [121]. Despite the positive cardiovascular effects of semaglutide, SUSTAIN 6 also revealed a higher-than-expected incidence of retinopathy complications (HR 1.76; 95%CI, [1.11 to 2.78]) and a higher incidence of treatment discontinuation as a result of gastrointestinal adverse events [120]. The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) study randomly allocated 9,901 individuals (46.3%

women), with T2D and either a previous CVD event or CVD risk factors to receive either dulaglutide or placebo with standard care [122]. The mean age of participants was 66.2 years and the median HbA_{1C} was 7.2%; MACE outcomes and all-cause mortality were recorded over a median follow-up period of 5.4 years [122]. Dulaglutide was found to significantly reduce the risk of MACE (HR 0·88; 95%CI [0·79–0·99]), but not all-cause mortality (HR 0·90; 95%CI [0·80–1·01]) in this population of people with T2D and CVD risk factors or prior CVD events [122].

1.2.9.6 Cardiovascular safety of SGLT-2Is

The mechanism behind the cardiovascular benefits of SGLT-2Is has yet to be fully elucidated, but it is thought to be due to pleiotropic effects [89]. At present, it is known that SGLT-2Is have effects on multiple processes beyond promoting glucose secretion, for example, they also enhance the oxidation of fats, reduce arterial stiffness, increase haemoglobin and haematocrit, reduce cardiac remodelling and fibrosis, promote body weight loss and promote uric acid excretion [89]

The Empagliflozin-Removing Excess Glucose (EMPA-REG OUTCOME) study was the first CVOT to demonstrate the unique set of cardiovascular benefits conferred a SGLT-2I [123]. This study, which enrolled 7,020 individuals for a median follow-up period of 3.1 years, found a reduction in the risk of the primary outcome, MACE, (HR 0.86; 95%CI, [0.74—0.99]), compared to standard care with placebo [123]. Empagliflozin did not change rates of MI or stroke, but it resulted in significant relative risk reductions for death from cardiovascular causes (HR 0.62; 95%CI [0.49—0.77]), HHF (HR 0.65; 95% CI [0.50—0.85] and all-cause mortality (HR 0.68; 95%CI [0.57—0.82]), compared to placebo [123].

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) randomised 17,160 individuals with T2D, who had or were at risk of ASCVD, to receive dapagliflozin or placebo with standard care [90]. The median follow-up time was 4.2 years [90]. DECLARE–TIMI 58 found similar benefits associated with dapagliflozin but less pronounced than for empagliflozin [90]. The risks of the combined outcome of cardiovascular death or hospitalization for heart failure (HR 0.83; 95% CI [0.73—0.95]) and HHF (HR 0.73; 95% CI [0.61—0.88]) were significantly lower than standard care plus placebo [90]. However, unlike empagliflozin, dapagliflozin did not reduce the cardiovascular death (HR 0.98; 95% CI [0.82—1.17]), MACE (HR 0.93; 95%CI [0.84—1.03]) or all-cause mortality (HR 0.93; 95%CI; [0.82—1.04]) outcomes [90].

The Canagliflozin Cardiovascular Assessment Study (CANVAS) randomised 10,142 people with T2D and high cardiovascular risk, (mean age 63.3 yeas, 35.8% women, 65.6% with a CVD history), to receive either canagliflozin or placebo with standard care [91]. The primary outcome was MACE, which was identified over a mean follow-up time of 3.6 years [91]. This study found that canagliflozin was associated with a 14% reduced risk of MACE, (HR 0.86; 95% CI [0.75—0.97]), but the risk of lower-limb amputations described in section 2.7 of this thesis has prevented this SGLT-2I from becoming widely used in Australia [91].

1.2.9.7 Cardiovascular safety of insulin

Despite its unmatched efficacy in reducing HbA_{1C}, insulin has been shown to increase the risk of cardiovascular outcomes and mortality among people with T2D [98]. Over-insulinisation is also associated with inflammation, atherosclerosis,

hypertension, dyslipidaemia, heart failure, and arrhythmias [98], which may all contribute to the mechanism by which insulin increases mortality and cardiovascular risk.

The Euro heart survey found that people with CHD and T2D who were treated with insulin had twice the risk of mortality HR 2.23 (95%CI [1.24—4.03]) compared to those treated with oral AHAs [124]. A post hoc analysis of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 trial noted that people treated with insulin were approximately 1.9 times as likely to experience a non-fatal cardiovascular event (OR 1.89 95%CI [1.35—2.62]) compared to insulin-treated patients who were swapped to conventional glucose control [125]. Finally, case-control study conducted in 2015 indicated that there may be a dose-dependent relationship concerning cardiovascular events and high (≥53.0 units per day), intermediate (24.3–52.9 units per day) versus low (≤24.2 units per day) insulin exposure [126]. This study noted that people who had experiences cardiovascular events were 3 times as likely (OR 3.00; 95%CI [1.70—5.28]) to be on a high dose, and twice as likely (OR 2.03; 95% CI [1.17—3.52]) to be on an intermediate insulin dose, compared to a low dose [126]. This study adjusted for confounders such as HbA_{1C} and triglycerides [126]. The UK Clinical Practice Research Datalink raised the prospect that the deleterious effects of insulin on cardiovascular outcomes may be at least partially mitigated by the addition of metformin [127]. In this study, adjusted HRs for people with T2D treated with insulin and metformin were associated with lower all-cause mortality (HR 0.60; 95% CI [0.52—0.68]), and MACE (HR 0.75; [0.62—0.91]), compared to insulin monotherapy [127].

In 2016, the ADA proposed a deconstruction and re-evaluation of current T2D guidelines, to make them more precise and patient centred [128]. In particular, it was proposed that patients should be assessed for their likely benefits from AHAs such as insulin, rather than being prescribed them by default in accordance with current treatment algorithms [128]. More recent ADA guidelines reflect this change in the T2D treatment paradigm through their inclusion of new sections which promote section of AHA based on individuals' CVD risk profile and comorbidities [129]. Because of the risks and practical challenges associated with insulin treatment, along with the clear cardiovascular and mortality benefits conferred by newer AHAs, it is unclear whether the future role of exogenous insulin in T2D will be anything other than as a last resort.

Table 1 Baseline Characteristics and primary composite cardiovascular outcomes from CVOTs

Trial (n)	**Intervention / control**	**Inclusion T2D**	**Mean age (years)**	**Mean BMI (kg/m^2)**	**Prior CVD/ CHF (%)**	**Median diabetes duration (years)**	**Mean HbA_{1C} (%) / HbA_{1C} change (%)**	**Median follow-up time (years)**	**Primary composite CV outcome (HR; [95% CI])**
SAVOR-TIMI 53 (n=16,492) [114,115]	Saxagliptin/ placebo	T2D with multiple risk factors for/ history of CVD	65.1	31.1	78/13	10.3	8.0/ -0.3	2.1	3-Point MACE 1.00 (0.89-1.12)
EXAMINE (n=5,380) [116]	Alogliptin/ placebo	T2D and ACS between 15-90 days before randomisation	61.0	28.7	100/28	7.1	8.0/ -0.3	1.5	3-Point MACE 0.96 (95% upper limit ≤1.16)
TECOS (n=14,671) [117]	Sitagliptin/ placebo	T2D and existing CVD	65.4	30.2	74/18	11.6	7.2/ -0.3	3.0	4-Point MACE 0.98 (0.89-1.08)
ELIXA (n=6,068) [84]	Lixisenatide/ placebo	T2D and acute coronary event within 180 days	60.3	100/22	100	9.3	7.7/ -0.3	2.1	4-Point MACE 1.02 (0.89—1.17)

Trial (n)	Intervention / control	Inclusion T2D	Mean age (years)	Mean BMI (kg/m^2)	Prior CVD/ CHF (%)	Median diabetes duration (years)	Mean HbA_{1C} (%) / HbA_{1C} change (%)	Median follow-up time (years)	Primary composite CV outcome (HR; [95% CI])
		before screening							
LEADER (n=9,340) [119]	Liraglutide/ placebo	T2D and pre-existing CVD and either kidney disease, HF (≥50 years of age) or ≥1 CVD risk factor (≥60 years of age).	64.3	64%	81/18	12.8	8.7/ -0.4	3.8	3-Point MACE 0.87 (0.78—0.97)
SUSTAIN-6 (n=3,297) [120,121]	Semaglutide / placebo	T2D and existing CVD, HF or CKD (≥50 years of age) or ≥1 CVD risk factor (≥60 years of age)	64.6	32.8	60/24	13.9	8.7/ -0.7	2.1	3-Point MACE 0.74 (0.58—0.95)
EXSCEL (n=14,752)	Exenatide QW/ placebo	T2D ± existing CVD	62.0	31.8	73/16	12	8.0/ -0.53	3.2	3-Point MACE 0.91 (0.83—1.00)

Trial (n)	Intervention / control	Inclusion T2D	Mean age (years)	Mean BMI (kg/m^2)	Prior CVD/ CHF (%)	Median diabetes duration (years)	Mean HbA_{1C} (%) / HbA_{1C} change (%)	Median follow-up time (years)	Primary composite CV outcome (HR; [95% CI])
[118]									
EMPA-REG OUTCOME (n=7,020) [123]	Empagliflozin / placebo	T2D and CVD, BMI≤45kg/m^2 and eGFR≥30ml/ min/1.73m^2	63.1	30.7	99/10	Not stated, 57% had a duration > 10 years	8.1/ -0.3	3.1	3-Point MACE 0.86 (0.74-0.99)
CANVAS (n=10,142) [87]	Canagliflozin / placebo	T2D and existing CVD (≥30 years of age) or ≥2 CVD risk factors (≥50 years of age)	63.3	32.0	66/14	13.5	8.2/ -0.58	2.4	3-Point MACE 0.86 (0.75-0.97)

CVOT Cardiovascular Outcomes Trial; SAVOR-TIMI 53 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI); EXAMINE Exenatide Study of Cardiovascular Event Lowering; TECOS Trial Evaluating Cardiovascular Outcomes with Sitagliptin; ELIXA Evaluation of Lixisenatide in Acute Coronary

Syndrome; LEADER Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6 Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL Exenatide Study of Cardiovascular Event Lowering; EMPA-REG OUTCOME Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; CANVAS Canagliflozin Cardiovascular Assessment Study; CVOT Cardiovascular Outcomes Trials; CVD cardiovascular disease; MACE major adverse cardiovascular event; ACS acute coronary syndrome; HF heart failure; CKD chronic kidney disease; BMI body mass index; eGFR estimated glomerular filtration rate.

Section 3: National and international guideline recommendations, and patterns of AHA prescribing and use

1.3.1 Guideline-recommended first-line treatment for T2D

Australian and international guidelines recommend that a diagnosis of prediabetes or a borderline positive test for T2D should first be managed with lifestyle changes such as smoking cessation, diet, weight loss and increased exercise [20, 130-132]. If glycaemic levels remain uncontrolled after 3 to 6 months, prescription of an AHA should be considered in order to prevent complications and death [20, 130-132].

The most recent clinical guidelines from the ADA and the European Association for the Study of Diabetes (EASD) recommend lifestyle modification and metformin monotherapy as initial pharmacotherapy for people newly diagnosed with T2D with HbA_{1C} levels less than 1.5 percentage units above target [62]. For asymptomatic individuals with HbA_{1C} 1.5 to 2.0 percentage points above target, ADA/EASD advise that dual therapy can be trialled immediately [62]. Here, dual therapy refers to the combination of two of the following AHAs: sulfonylurea, thiazolidinedione, DPP-4I, SGLT-2I, GLP-1 RA, or basal insulin, preferably combined with metformin, if not contraindicated [62]. Insulin therapy can also be initiated in addition to one of the aforementioned AHAs if HbA_{1C} >10%, BGLs ≥300mg/dL or if an individual is symptomatic [62].

The American Association of Clinical Endocrinologists (AACE) has similar recommendations with regards to initial T2D therapy but suggests lifestyle therapy with metformin (where not contraindicated), for mild hyperglycaemia (HbA_{1C} ≤7.5%).

Dual therapy can be initiated when HbA_{1C} is between 7.5% and 9.0%, and is recommended to include two of the following drugs with complementary mechanisms of action: metformin, GLP-1RA, SGLT2-I, DPP-4I, thiazolidinedione, acarbose, sulfonylurea, basal insulin or a glinide [133]. For individuals who are symptomatic with HbA_{1C}>9.0%, dual therapy plus insulin, (triple therapy), can be initiated [133]. Recent changes to AACE guidelines have included a recommendation to prescribe long acting GLP-1RAs or SGLT-2Is for all individuals at high ASCVD risk or with CKD, regardless of BGLs or T2D treatment stage [133].

The Royal Australian College of General Practitioners have published clinical practice guidelines, which recommend metformin as a first-line, PBS-subsidised treatment for T2D. Sulfonylureas are also guideline recommended in Australia as a PBS-subsidised alternative for individuals who cannot tolerate or have contraindications against metformin [20]. Combination therapy at the point of T2D diagnosis is not addressed in Australian guidelines, regardless of HbA_{1C} levels, however, like the ADA/AACE guidelines, the RACGP recommends the stepwise addition of an AHA after 3-6 months if HbA_{1C} levels continue to be above target [20].

Benefits of a stepwise approach to initial therapy include having a greater ability to individualise treatment, improved adherence, fewer adverse drug events and lower cost [134]. Conversely, initial combination therapy can reduce patients' time above ideal glycaemic levels, delay disease progression, target multiple pathophysiological mechanisms and reduce clinical inertia [134].

1.3.2 Prescribing patterns for first-line T2D pharmacotherapies

An Australian study from 2000-2008 found that a relatively high proportion of AHA initiations included sulfonylureas (42%) [135]. More recent Australian data shows that sulfonylurea initiations only constituted 12% of AHA initiations from between 2006 and 2014 [136]. The study also showed that during these years, 83% of AHA initiations involved metformin [136]. This reflects a trend towards sulfonylureas becoming a less favoured, and metformin becoming a more favoured option for initial treatment of T2D in Australia, which can be also seen internationally [137].

Patterns of AHA use in the USA mirror the trends seen in Australia over the past decade. Of particular note is that the proportional share of AHA initiations involving metformin rose from 60 to 77% between 2005-2016 while the share of sulfonylureas declined from 20% to 8% over the same period (Figure 3). A European study which compared AHA initiations between four countries, (UK, Spain, The Netherlands [NL] and Italy), found that sulfonylureas were more likely to be used first-line in older people >75 years (2.0 to 3.7 times as likely than in people ≤75 years), and in those with renal comorbidities (2.5 times as likely in NL and UK) [138]. In the UK and Spain there was an inverse association between sulfonylurea use and Body Mass Index (BMI) [138]. These results are likely to reflect contraindications against metformin in older people, particularly those with severe renal impairment as well as the tendency of sulfonylureas to cause to cause weight gain.

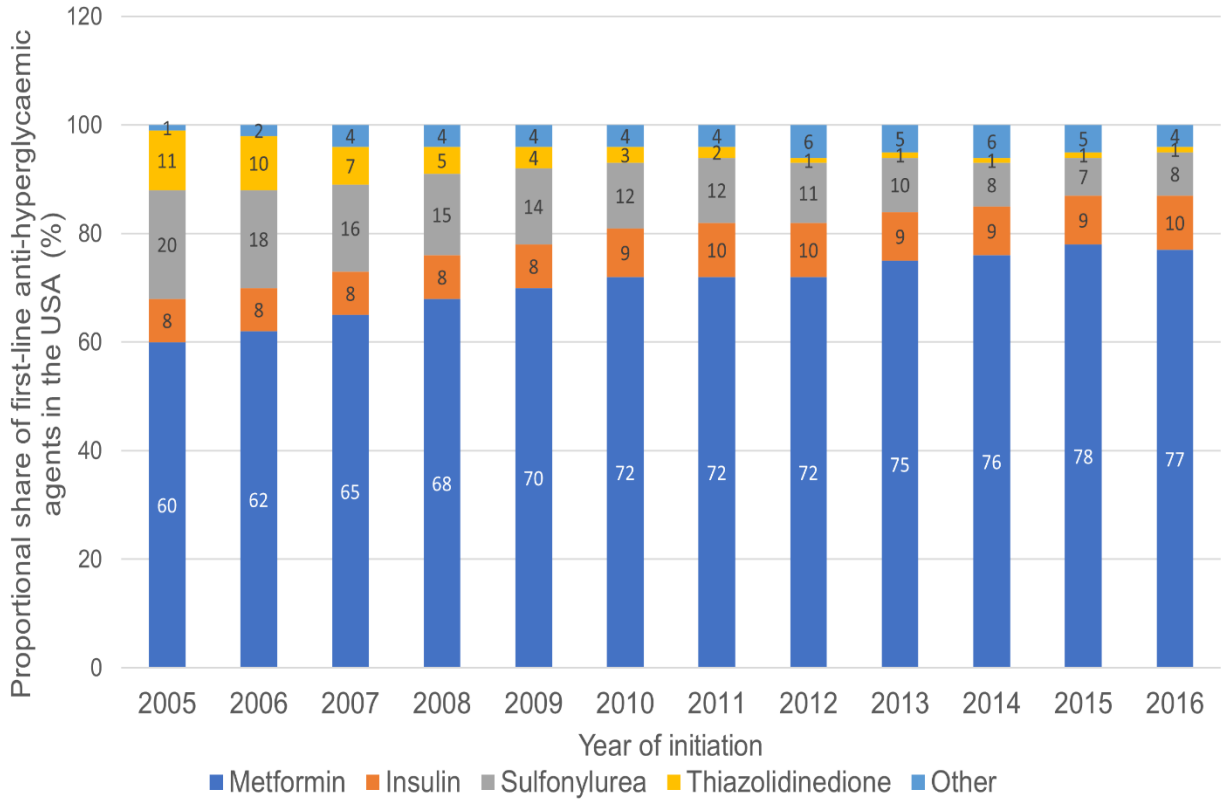

Figure 3: Proportional share of first AHA by year of initiation in the USA. Adapted from [139].

1.3.3 Clinical inertia and treatment progression

In Australia, people with T2D should have contact with a GP on a three- to six-monthly basis. During these consultations, GPs review individuals' lifestyle factors, mental health, comorbidities and intercurrent illnesses [20]. In addition, they will likely review AHA medication regimens, check for the presence of hypoglycaemia and may conduct an HbA_{1C} test to assess overall glycaemic control over the previous three months [20]. If it is deemed necessary, an AHA may be added or switched. Clinical inertia is defined as the failure to initiate or intensify treatment, despite the clinician's awareness of clinical guidelines which recommend that it is appropriate [140].

Clinical inertia is not always easy to identify as prescribers intentionally delay or avoid adding new medications for some individuals with T2D because their glycaemic targets may be less stringent. Three major reasons for this pertain to physician, patient, and healthcare factors [140]. Physician factors are thought to be associated with 50% of clinical inertia instances and may occur with the decision to delay initiation or intensification of treatment due to underestimation of patients' needs, insufficient consultation time or reactive, rather than proactive patient care [140]. Patient factors, which contribute 30% to clinical inertia, may relate to denial of the severity of T2D, cost of treatment, lack of trust in the physician, low health literacy or the presence of complex health conditions, especially mental health problems [140]. Finally, healthcare related factors, which are only thought to explain 20% of clinical inertia, may relate to deficiencies in decision support, staff-practitioner communication, financial incentives, active outreach, or healthcare team dynamics [140].

Timely treatment intensification in T2D has been shown to be associated with a significantly greater likelihood of patients achieving good glycaemic control (HbA_{1C} <8.0%) [76] and decreases the time to achieve glycaemic control, regardless of whether treatment initiation was on metformin or a sulfonylurea [141]. An Australian study of a veteran population with T2D, conducted between 2000 and 2008, found that an increasing number of comorbidities was associated with delays in treatment additions or switches after initial monotherapy [135]. This study also found that individual conditions such as depression, cancer, chronic obstructive pulmonary disease, dementia, and Parkinson's disease as well as age, medication adherence and number of hospitalisations were all associated with a decreased likelihood of

therapeutic progression. This study found that in this Australian veteran population approximately 24% of individuals had their treatment progressed (receiving either an additional medication or a switch) after one year and 41% progressed after four years [135]. This study did not provide a breakdown of which AHAs were received as part of treatment progression.

Another Australian study of older, socioeconomically disadvantaged Australians with T2D found that 83% of AHA initiations involved metformin and that the average time until a second AHA was initiated was 4.8 years [136]. Factors identified in this study which predicted the initiation of another AHA were initiation of therapy prior to 2012, male sex, initiating treatment with a sulfonylurea and adherence to therapy [142]. The latter result could be explained by more adherent individuals having closer contact with their general practitioners and thus, more opportunities for addition of therapy [136].

A study of electronic health records across four European countries (UK, Spain, Italy and the NL) conducted between 2007 and 2012 found that 79% of the treated T2D population had their AHA therapy intensified within 5 years [138]. In three of the four countries (UK, Spain, NL) a trend towards decreased use of thiazolidinediones and increased use of DPP-4Is was observed over the duration of the study [138].

With respect to the initiation of second line therapies, Australian and ADA/EASD guidelines are relatively similar [20, 130]. Real world evidence examining second line AHA prescribing in the USA after first-line treatment with metformin (Figure 4) shows that sulfonylureas were the most commonly prescribed second line AHA between

2005 and 2016, but the proportional share reduced from 60% to 46% during this period [139]. There was also a marked reduction in the proportion of second line AHA recipients who were prescribed a thiazolidinedione between 2005 (30%) and 2016 (4%), which is likely to reflect the 2007 CVOT concerning the cardiovascular risks of rosiglitazone [106, 139]. In the same study the prescribing of second line agents which were not used prior to 2005, such as DPP-4Is, GLP-1RAs and SGLT-2Is, increased such that these medications constituted 20%, 7% and 7% respectively, of all prescribed second line pharmacotherapies in the USA in 2016 [139]. Despite the increased numbers of DPP-4Is added to metformin monotherapy in recent years, a retrospective study by Mamza et. al. found that the addition of either a sulfonylurea or thiazolidinedione to metformin provided longer term blood glucose control, compared to the addition of a DPP-4I [143]. Lower rates of treatment failure of sulfonylureas and thiazolidinediones may partially explain why some clinicians continue to prescribe them as second line therapies.

The prescribing of an AHA does not necessarily mean that the medication will be used as intended, and treatment failure may be attributable to non-adherence. Certain populations, particularly those with mental health problems such as depression [144] or schizophrenia are known to have lower rates of adherence to AHAs [145]. One large Australian cohort study demonstrated that individuals initiating AHAs with a recent history of receiving antidepressant medications were 42% more likely to discontinue their AHA than those who did not receive antidepressants [144]. Similarly, a cohort study in Quebec found that people newly diagnosed with T2D with a history depression had 24% higher adjusted odds of being nonadherent, compared to people without a depression diagnosis [146]. The

Australian National Diabetes Audit (ANDA) found that approximately one in three people with T2D who attend diabetes centres were living with depression and diabetes distress [147]. Diabetes distress relates to the emotional toll of diabetes management which is distinct from other causes of emotional distress or mental health problems [147]. The study also found that both depression and diabetes distress have a negative impact on adherence to self-care regimes and that this can contribute to higher HbA_{1C} levels [147]. A systematic review of people with both T2D and schizophrenia, found that adherence to diabetes medications was between 51-85% [145]. This research acknowledges the limitation that the majority of people included were men >50 years and suggests that further research into T2D medication adherence is needed for women, younger people and those who have recently been diagnosed with T2D [145]. These studies demonstrate that sometimes treatment failure occurs in people with T2D because of patient related factors rather than because of a lack of medication efficacy.

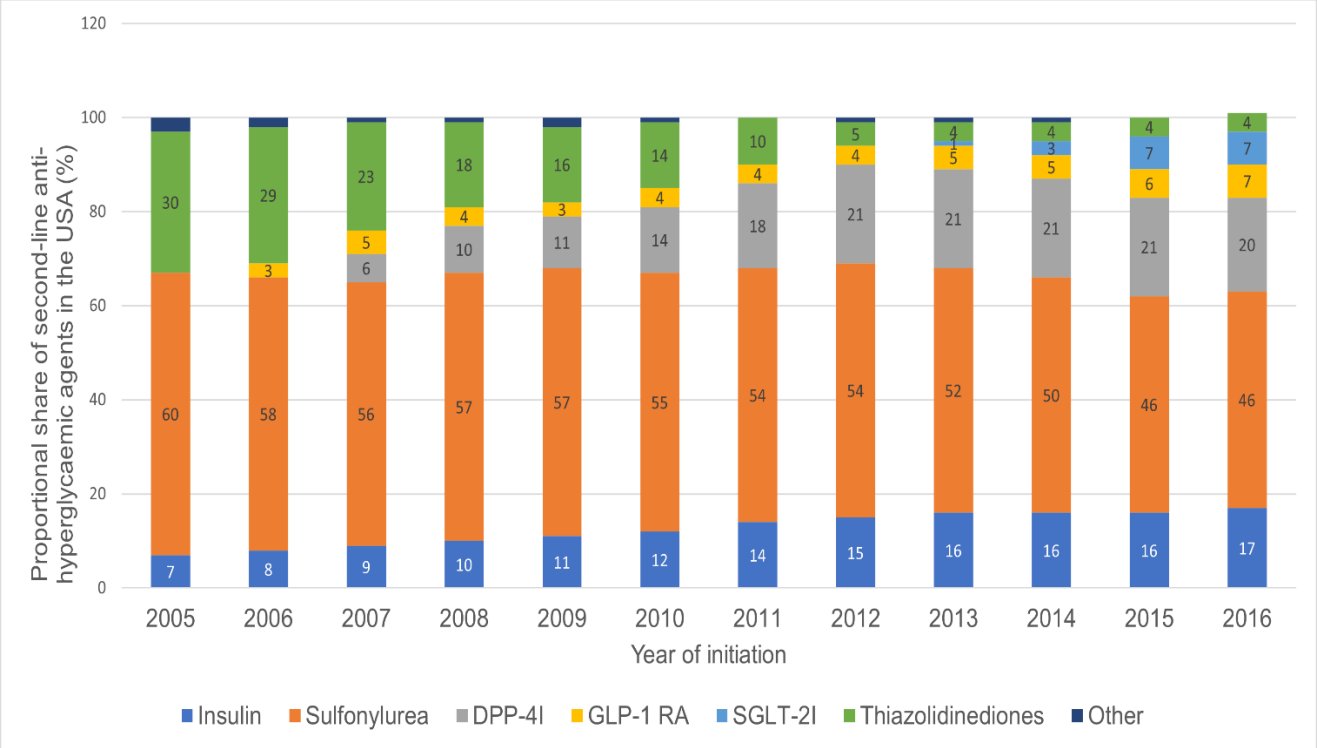

Figure 4: Proportional share of second-line AHAs by year of initiation in the USA. Adapted from [139].

With respect to the guideline recommended pharmacological treatment of T2D, there are important gaps in the research literature. Firstly, the patterns of medication initiation for T2D, to the best of our knowledge, have not been previously published. The predictors of being initiated on metformin or another T2D therapy have not been explored in Australia. In addition, there is a lack of studies conducted in Australia since 2008, which explore predictors of treatment progression from first-line monotherapy, and which distinguish treatment additions from switches. These topics will be investigated in detail in Chapter 2 and Chapter 3, contained within the results section of this thesis.

1.3.4 Variations in Australian and International AHA prescribing

Over the last decade there have been significant changes in prescribing patterns of AHAs in Australia and internationally. A retrospective study of primary care data which included Australia, Canada, Scotland and England has shown similar trends in the prescribing of AHAs across these countries between 2012 and 2018 [82]. In all four countries there was a steady increase in the dispensing of DPP-4Is and GLP-1RAs as well as an exponential increase in the uptake of SGLT-2Is [82]. The absolute percentage increases in the proportion of people receiving AHAs who were prescribed these classes in Australia between 2012 and 2018 were 12.6%, 2.9% and 15.3%, respectively [82]. The prescribing of thiazolidinediones either remained at very low levels (Australia and Scotland) or decreased sharply from an already low baseline (Canada and England) [82]. There were also sharp decreases in the proportion of AHA recipients who were prescribed sulfonylureas across time in Australia, Canada and England, with an absolute percentage reduction of 8.8% in Australia [82].

A notable difference between the prescribing patterns of these four countries was that the percentage of people on AHAs who received metformin rose in Australia (85.5% to 88.9%), whereas it declined in Canada (83.8% to 79.1%) between 2012 and 2018 [82]. This could reflect increasing rates of non-metformin AHAs being prescribed as initial treatment in Canada or a higher rate of metformin deprescribing in Canada, compared to Australia. The proportions of AHA recipients prescribed metformin in England and Scotland were 90% and 91%, which remained relatively stable between 2012 to 2018 [82].

Aside from changes over time, there are also differences in AHAs receipt, particularly amongst disadvantaged groups [148]. An Australian study by Morton et al. found that there are disparities in prescribing newer AHAs between socioeconomic strata [148]. This large study of approximately 1.2 million Australians with T2D found that people in the most versus the least disadvantaged quintiles were less likely to be dispensed DPP-4Is, (OR 0.78; 95%CI [0.75—0.82]), GLP-1RAs (OR 0.65; 95%CI [0.60—0.71]) or SGLT-2Is (OR 0.89; 95%CI [0.84—0.95]), during the first year of their availability [148]. This study also found that people in the most remote areas versus major cities were also less likely to receive DPP-4Is, (OR 0.46; 95%CI [0.39—0.54]), GLP-1RAs (OR 0.46; 95%CI [0.35—0.61]) or SGLT-2Is (OR 0.71; 95%CI [0.59—0.84]), and that these differences remained until the study ended in 2015 [148].

Section 4: Use and outcomes of AHAs in vulnerable populations

1.4.1 The interrelationships between hypoglycaemia, frailty, and dementia

Whist meeting glycaemic targets is important in terms of preventing vascular events, complications and death, it is also critical that these targets are individualised to reflect the health status of the person with T2D [20, 149]. As discussed in Section 1, the ACCORD trial demonstrated that excessively tight glycaemic control can result in considerable harms and can increase the risks of macrovascular events and death [64]. One population which has been shown to be at an elevated risk of harm from T2D overtreatment is people who are frail [150]. Although it can be defined differently by other tools, frailty is characterised by Fried by the presence of ≥3 of the following: weight loss, weakness, decreased physical activity, exhaustion or slow gait speed [151]. The condition is also marked by increased vulnerability to adverse health outcomes resulting from a depletion of physiological reserve [152]. People who are frail are also more likely to have a limited life expectancy, serious comorbidities and a high risk of hypoglycaemia from sulfonylureas and insulin [153]. As depicted in Figure 5, the RACGP guidelines suggest the relaxation of glycaemic targets for individuals who may experience greater risks and more limited benefits from intensive glycaemic control.

Frailty has also been shown to be the strongest predictor of mortality, disability and institutionalisation amongst older adults [154]. Using the 5-component Fatigue, Resistance, Ambulation, Illness, and body weight Loss, (FRAIL) scale, Chao et al. reported that after 3.1 years, those with a FRAIL score ≥3 had a 25% increased risk or mortality or hospitalisation and a 13% increased risk of a cardiovascular event,

compared to those with a FRAIL score of 0 [153]. This study also noted a 6-7% increase in risk of mortality and healthcare utilisation for every 1 frailty component increase in FRAIL score [153]. Ferri-Guerra et al. reported a 70% increase in the risk of hospitalisation and a doubling of the risk of mortality after 561 days amongst a veteran population ≥65 years of age who were frail, compared to those who were robust [150].

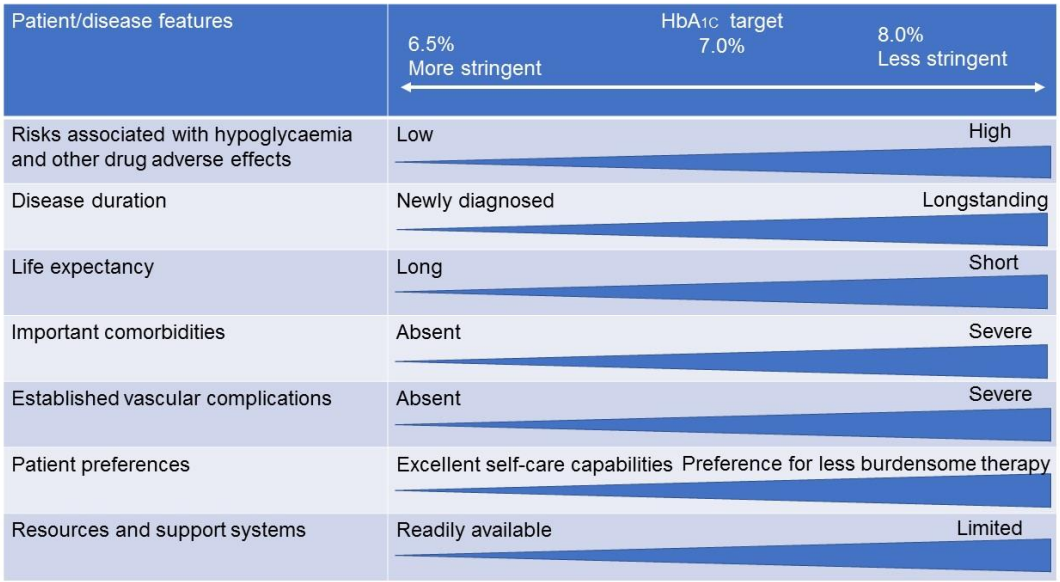

Figure 5: Stringency of Glycaemic targets recommended by RACGP, based upon patient characteristics. Adapted from [20].

There are important and reciprocal relationships between frailty, hypoglycaemia and dementia [17]. Frailty can be exacerbated by overly stringent glycaemic targets and the use of medications linked with hypoglycaemia [17]. This is of particular concern as many AHAs which are known to induce hypoglycaemia, such as sulfonylureas and insulin, are routinely prescribed for older people. A US study of 19,932 people enrolled in Medicaid aged ≥65 with diabetes estimated that the crude rates (per 100 person-years) of serious hypoglycaemia were 1.23 (95%CI [1.08—1.38]) in sulfonylurea users and 2.76 (95%CI [2.47—3.06]) among insulin users [155]. Rapid

HbA_{1C} reductions from ≥7.5% at baseline to <7.5% after one year have also been linked to the development of dementia in people with T2D [156]. A retrospective cohort study from the UK conducted between 2003 and 2012, found that individuals >65 years with newly diagnosed T2D and either one hypoglycaemic episode or two or more episodes had 26% (HR 1.26; 95%CI [1.03—1.54]) and 50% (HR 1.50; 95%CI [1.09—2.08]) increased risks, respectively, of developing dementia, compared to those without recorded hypoglycaemia [157]. The median follow-up time in this study was 3.8 years (interquartile range [IQR] [1.8–6.3 years], whilst the median time from the first episode of hypoglycaemia until dementia was 1.8 years (IQR [0.8—3.8 years]) [157]. It is possible that this study had an insufficient follow-up time as dementia takes many years to develop.

T2D is associated with premature aging and earlier development of geriatric phenotypes [153]. T2D also confers a higher risk of developing dementia for people who already have mild cognitive impairment [158]. However, people with dementia and comorbid T2D have a higher risk of developing hypoglycaemia with coma, depression, hypertension, stroke, diabetic foot syndrome and microalbuminuria, compared to those with T2D without dementia [159]. These conditions can further contribute to frailty.

It has been shown in several European countries that people with advanced age and renal comorbidities had greater odds of receiving sulfonylurea and insulin combinations as third-line therapy, (UK, Spain, NL), despite the significant risk of hypoglycaemia and falls in these population groups [138]. A systematic review has also found that those who are older, frail and have multiple comorbidities are more

likely to be overtreated with AHAs and noted that current clinical guidelines emphasise prevention of underuse rather than overuse of AHAs [160]. People who may benefit from deintensification of AHA therapy are older people, people with difficulties in activities of daily living and those with multiple complex comorbidities, especially dementia and chronic renal disease [160]. It has also been found that deintensification of AHA therapy, specifically insulin and sulfonylureas, can be feasible, without deteriorations in glycaemic control and with risk reductions for future episodes of hypoglycaemia and reduced diabetes related distress scores [160].

The extent to which older and more frail populations are prescribed “higher risk” AHAs, especially insulin combined with additional AHAs, has previously been challenging to study in the hospital setting; however, the recent introduction and validation of a Hospital Frailty Risk Score (HFRS), has made frailty readily quantifiable in this setting [161]. This research will be described in detail in Chapter 4, contained within the results section of this thesis.

1.4.2 Prescribing and use of newer and potentially beneficial AHAs for vulnerable populations

The increased uptake of SGLT-2Is in recent years, as was highlighted in Chapter 1, Section 3, likely reflects prescribers' recognition of the significant risk reductions in hospitalisation for heart failure HHF and mortality observed in the SGLT-2I CVOTs [90, 91, 123]. An important limitation of the evidence generated from RCTs regarding the efficacy and safety of AHAs is that they often exclude individuals with very poor health status. This can yield results which are not an accurate reflection of the real world T2D population.

Whilst CVOTs did not quantify frailty levels at baseline, a recent systematic review of major CVOTs has estimated the risks of cardiovascular events amongst subpopulations with conditions prevalent in frailty, such as ASCVD, CVD and CHF [162]. With respect to SGLT-2I outcomes, it was reported that those with established ASCVD (HR 0.86; 95%CI [0.77—0.96]) or CVD (HR 0.85; 95%CI [0.76—0.96]), had lower risks of 3P-MACE, compared to placebo [162]. It was also found that people with CHF had a lower risk of HHF (HR 0.61; 95%CI [0.50—0.76]) and those with heart failure (HR 0.81; 95%CI [0.72—0.91]) were less likely to experience the combined outcome of cardiovascular death or HHF [162]. People with CKD at baseline were less likely to develop the combined renal outcome (HR 0.64; 95%CI [0.59—0.70]), which included progression to albuminuria >300 mg/g, doubling of serum creatinine, GFR < 15 ml/minute/1.73 m^2, need for dialysis, renal transplantation, or death due to renal causes [162]. It was noteworthy that in this systematic review, which did not include the CANVAS study, SGLT-2Is were not found to confer a statistically significant benefit with regard to 3P-MACE for

individuals ≥ 65 years [162]. Another systematic review and meta-analysis, which included the CANVAS study reported a modest reduction in 3P-MACE outcomes from SGLT-2Is (HR 0.83; 95%CI [0.71—0.96]) in those aged ≥65 years [163].

In a systematic review of SGLT-2I RCTs conducted by Gebrie et al., metformin combined with an SGLT-2I rather than with a sulfonylurea was found to provide benefits across numerous outcomes, including HbA_{1C} reduction (mean difference [MD] = −0.10%; 95% CI [−0.17, −0.03]), body weight (MD = −4.57 kg; 95% CI [−4.74, −4.39]), systolic blood pressure (MD = −4.77 mmHg; 95% CI [−5.39, −4.16]), diastolic blood pressure (MD = −2.07 mmHg; 95% CI [−2.74, −1.40]), FPG (MD = −0.55 mmol/L; 95% CI [−0.69, −0.41]), and hypoglycaemia (RR 0.13; 95% CI [0.10, 0.17]) [9].

Real world studies such as the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) and the CVD-REAL-2 study [164, 165] have examined the outcomes of SGLT-2I use in the real world setting across multiple countries. These studies have all provided directionally similar results with even lower relative risks for outcomes such as HHF and death than were estimated in CVOTs. The original CVD-REAL study included data from medical claims, primary care or hospital records as well as national registries from the USA, Norway, Denmark, Sweden, Germany, and the UK [164]. In this analysis, a considerable reduction in risk of the composite outcome of HHF or death (HR, 0.54; 95%CI, [0.48–0.60]) was reported [164]. An analysis of the CVD-REAL study revealed that reductions in HHF and death were similar regardless of CVD status at baseline [164, 166] Similarly the CVD REAL-2 study, which included several

countries from the Middle East, North America and Asia Pacific (including Australia), found statistically significant risk reductions for death, HHF and stroke when SGLT-2Is were initiated rather than other AHAs [165]. Maximum risk reduction was observed when data were pooled was for the composite outcome of HHF or death (HR 0.60; 95%CI [0.47-0.76]) [165].

Despite the known advantages of SGLT-2Is for people with CVD, they are still prescribed relatively infrequently in many countries, compared to sulfonylureas [82]. Arnold et.al. have also reported that between 2014 and 2016 in the USA, patients prescribed thiazolidinediones tended to be older (mean age, 69.2±10.7 years), and substantial proportions had CHD (61.9%), heart failure (23.7%), class 3 obesity (17.2%), or an ejection fraction <40% (7.7%) [167]. Cosmi et al. have also shown that the use of insulin in people with T2D and heart failure is associated with poorer health outcomes, yet it continues to be prescribed for these individuals [168]. Therefore, there are indications that best practice guidelines may not be observed with respect to clinicians treating people with CVD and T2D [62].

Currently, the ADA/ EASD guidelines recommend the prescribing of SGLT-2Is for people with a history of heart failure, which is in line with the systematic reviews and large-scale observational studies described above. It could be hypothesised that people with complex health conditions associated with frailty could also derive benefits from the use of SGLT-2Is, however, there remains a lack of evidence for the use of these medications in populations such as these. The focus of Chapter 5 is on the outcomes of MACE, HHF and all-cause mortality in frail populations. This analysis investigates whether the cardiovascular and mortality benefits of SGLT-2Is

in frail populations with T2D are similar to those observed in the general T2D population.

Section 5: Data sources and Aims

1.5.1 Description of data sources used in this project:

The two national databases used in this PhD were the 10% Random Sample of the PBS Dataset and the National Diabetes Services Scheme (NDSS) – PBS Linked Dataset. Additionally, there were two hospital databases used, namely, the Eastern Health Dataset and the Victorian Admitted Episodes Dataset (VAED). The latter is also linked to medication dispensing data via the PBS. Tables 2 and 3 summarise the key strengths and weaknesses of the data sources.

1.5.1.1 The 10% random sample of the Pharmaceutical Benefits Scheme (PBS) Dataset

The 10% random sample of the PBS contains claim for payment information issued by pharmacies in Australia from 2006 to date. All Australian citizens, permanent residents and people from countries with reciprocal health care agreements are entitled to receive general PBS reimbursement [169]. This dataset contains PBS item codes, dispensed strengths, dispensed quantities, dates of prescribing and dates of supply as well as recipients' year of birth, year of death and sex. PBS item codes can be mapped to the Anatomical Therapeutic Chemical (ATC) codes commonly used in pharmacoepidemiological research. These codes classify drugs according to the body system on which they act, then further categorises them based on their therapeutic class and molecular structure. Therefore, ATC codes are useful in identifying both specific AHAs as well as classes of AHAs.

A strength of this dataset is that it is nationally representative and generalisable [169]. It also contains dispensing information for under co-payment items dispensed after July 2012. Limitations of the dataset include a lack of clinical and laboratory results such as glycated haemoglobin HbA_{1C} and that it does not contain information about medicines which were accessed through non-PBS avenues. In addition, whilst it is known that the items were dispensed, it is not known whether they were taken by the people for whom they were prescribed [170].

1.5.1.2 National Diabetes Services Scheme (NDSS) – PBS linkage

The NDSS provides subsidised access to various products used in the management of diabetes. NDSS registrant data are held by Diabetes Australia, under the custodianship of the Australian Government Department of Health [171]. Registration on the NDSS is optional and takes place after a confirmed diabetes diagnosis. The NDSS register contains demographic and diabetes related information between 1987 and 2016 including sex, date of birth, date of diabetes diagnosis, date of death (via a linkage to the National Death Index), SEIFA (Socio-Economic Indexes for Areas) score, ARIA (Accessibility/Remoteness Index of Australia) score and diabetes type. Since the AIHW linked the NDSS data with PBS data, information about medications supplied to individuals on the PBS, (see above) is also available. Linkage was conducted using probabilistic matching, which is based on partially identifying variables such as name, age and sex. Linked data containing under co-payment dispensing records dated from July 2012 until April 2015. Access to the NDSS-PBS data required the use of the SURE (Secure Unified Research Environment), which is a computing environment protected by both a password and time sensitive token.

The NDSS captures between 80-90% of all people in Australia [171] who have diabetes. Regular cleaning of the data occurs in order to eliminate duplicate records and other redundant information. This dataset is also specific for people with diabetes since people can only be registered on the NDSS by a medical practitioner or certified diabetes educator after a confirmed diagnosis of diabetes. Limitations are similar to the PBS dataset (see above) and include the fact that people with undiagnosed diabetes will not be included and, in addition, there is a poor representation of Australian and Torres Strait Islander people. The diabetes type classification is completed by the diabetes educator or GP at time of registration, and it is also possible that misclassification of diabetes type could occur. Therefore, for this project, we applied to more stringent algorithm to type registrants into type 1 and type 2 diabetes, who would increase certainty of diabetes type. In brief, in the NDSS dataset, T1D status is only assigned to registrants classified by a health professional as having T1D in addition to being diagnosed before the age of 30 years, and with a time between diabetes diagnosis date and date of insulin initiation being <1 year [172]. For people with missing dates of diabetes diagnosis or insulin initiation, T1D was only recorded for those classified as having T1D on the registry in addition to taking insulin and being ≤45 years of age [172]. Those on the NDSS not fitting the criteria for designation of T1D were deemed, by default, to have T2D [172].

For those missing data on date of diagnosis or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as T1D if they were recorded as such on the registry, were taking insulin, and were registered at ≤45 years of age. We chose 45

years as the cut-off to minimize the number of people with T1D that we would miss, without misclassifying significant numbers of people with T2D as T1D.

1.5.1.3 Eastern Health Dataset

The Eastern Health (EH) Dataset contains discharge prescribing data from all 7 Eastern Health Hospital locations in and around Melbourne. The EH network includes 3 acute and 4 subacute hospitals with 1,423 beds and services a catchment area of around 750,000 people of diverse backgrounds [173]. EH has routinely utilised electronic prescribing since 2011. This process involves physicians producing a complete prescription containing all medications intended for patient use after discharge within an Electronic Medical Record (EMR) [173]. EMRs are generally created within 24 hours before patient discharge [173]. The dataset contains demographic variables including age and sex. There are also data regarding the separation type, date of admission, date of separation (discharge) and length of hospital stay (in days). Importantly, information about the diseases with which patients have been diagnosed, in the form of International Classification of Diseases 10th Edition (ICD-10) codes. These codes are frequently used in pharmacoepidemiological research to identify diagnosed medical conditions and the codes are updated when changes are made to the way diseases are categorised [174]. The EH dataset was established and cleaned by Dr Laura Fanning in a similar manner to that described in a previous publication [175]. Obtaining the cohort involved identifying individuals discharged with an ICD-10 code indicating T2D as a primary or secondary diagnosis or an associated condition. Subsequently, inter-hospital transfers were merged into single episodes of care and people with a discharge code indicative of death were excluded. The medications prescribed upon discharge from EH, as recorded in the hospital's electronic medication records, were available in the dataset, but subsequent community dispensings were not.

Advantages of this dataset include that it provides information about all EH admissions between 2012 and 2016 and that associations between exposure to initial discharge medications and time to rehospitalisation can, therefore, be assessed. The discharge prescribing data have been shown to validly predict the actual medications dispensed to patients with diabetes [173]. Limitations of the EH dataset include a lack of clinical information such as HbA_{1C}, the fact that results may not be generalisable to all people with diabetes and that it cannot be assumed that patients will take their medications as prescribed. In addition, surgical patients with a length of stay less than 24 hours do not receive a complete list of all medications upon discharge [173].

1.5.1.4 Victorian Admitted Episodes Dataset (VAED) linked to the PBS and the National Death Index (NDI)

The VAED contains demographic, clinical and administrative details regarding patients admitted to all public and private hospitals, rehabilitation centres, extended care facilities and day procedure centres in the state of Victoria [176, 177]. This dataset contains records for over 331,000 people who were discharged from a Victorian hospital between July 2012 and June 2018 with a diagnosis of diabetes. Since June 30, 1998, diagnoses have been recorded using ICD-10 codes. The Victorian Hospital Admission Policy substantially changed in 2012/2013 [177], and after this time, the admission dates for patients admitted through the Emergency Department (ED) were based on times of admission, rather than times of presentation at the ED [176, 177]. Demographic variables contained in the dataset include age, sex, postcode, suburb and country of birth. There are also

administrative data regarding the separation type, date of admission, date of separation (discharge) and length of hospital stay [177]. The VAED was linked to the Medicare Enrolment File (MEF) using probabilistic matching techniques. First, the Centre for Victorian Data Linkage (CVDL) provided the AIHW with data on a cohort of individuals >30 years of age hospitalised in Victoria with an ICD code indicating hip fracture, diabetes, ischaemic stroke or MI. Variables contained in this dataset which were used to match with the MEF included surname, three other name fields, date of birth, date of death address, postcode and sex. These were then assigned weights indicating the probability of a true match with MEF data, based on information agreement. After a sample-based clerical review using a comparison weight cut-off of 30.0022, the match link rate was 99.48% and the link accuracy was 99.76%. A merger was then used to extract MBS, PBS and NDI data for the 419,142 people with acceptable record pair matches.

Advantages of this dataset include that it provides information about all Victorian hospital admissions during the study period and that a cohort of people hospitalised for T2D can be obtained. Times to rehospitalisation, death, or the development of a health outcome of interest can be assessed using the linkages to the National Death Index (NDI), PBS and Medical Benefits Scheme (MBS) datasets. Limitations of this dataset include a lack of laboratory results such as HbA_{1C} and that results may not be generalisable to the broader population of people with diabetes because all members of the cohort were initially hospitalised.

Table 2 Strengths and limitations of the national datasets used in this PhD which capture people with T2D

	The 10% random sample of the Pharmaceutical Benefits Scheme (PBS)		**National Diabetes Services Scheme (NDSS)— PBS Dataset**	
	Strength	Limitation	Strength	Limitation
Breadth of data capture	PBS captures most dispensed prescriptions in Australia.	Only a 10% sample of people dispensed PBS medications.	Captures 80-90% of all people with diabetes.	Cannot capture those with undiagnosed diabetes or those who are not enrolled in the NDSS
Hospital dispensings	Includes discharge and outpatient PBS dispensings from public hospitals in most Australian states.	Does not include hospital dispensings in New South Wales and Australian Capital Territory.	As for PBS 10% sample	As for PBS 10% sample
Representativeness of data	Representative of and generalisable to the wider Australian community	Includes few sociodemographic variables, making it difficult to draw conclusions about sub-populations based on rurality or socioeconomic status.	Provides dispensing records for all NDSS-enrolled individuals	NDSS-PBS linked dataset is not considered to be representative of Aboriginal and Torres Strait Islander community
Available data	Individual-level data including age, sex, year of birth, year of death, derived prescriber speciality,	PBS item codes can change over time and there is a lack of data on expected duration of a supply of the indication for use	As for PBS 10% sample	As for PBS 10% sample

	patient category (e.g., concessional), PBS item codes for medicines	Lack clinical and laboratory results		
Monitoring of ongoing medication use	Allows for follow-up of up to several years (2006 to 2020)	Does not contain information about prescribed dose or expected duration of prescription, making it difficult to distinguish continued use from cessation.	Allows for follow-up of up to several years (2006 to 2016)	As for PBS 10% sample
Bias	Reduced potential for attrition bias, reporting bias or loss to follow-up	Cannot be assumed that patients take dispensed medications as prescribed.	As for PBS 10% sample	As for PBS 10% sample

Table 3 Strengths and limitations of datasets including hospitalised people

	Eastern Health (EH) Dataset		Victorian Admitted Episodes Dataset (VAED)-PBS-NDI linked dataset	
	Strength	Limitation	Strength	Limitation
Breadth of data capture	EH dataset provide five years of discharge prescribing data from a large public hospital network in Melbourne.	EH dataset is not linked to PBS so medications dispensed in the community are unknown	VAED dataset provides hospitalisation data from all Victorian hospitals, both public and private. VAED dataset is also linked to the PBS.	Pathology data not available.
Generalisability of data	Represents a network of many individual hospitals across Melbourne and is likely to be comparable to hospital networks in other large, developed cities.	Other hospital networks may have different policies and procedures	All Victorian hospitals	Can only be used to generalise to Victorian hospitalised patients; not to other states or the broader community.
Available data	Inclusion of ICD-10 codes makes it possible to identify comorbidities associated with hospitalisation. Medicine codes allow identification of medication dispensed on discharge	Does not contain information about medication dispensed before or after discharge.	Inclusion of ICD-10 codes makes it possible to identify comorbidities associated with hospitalisation. Link to ATC codes (mapped through PBS item codes) from the PBS allows for identification of community dispensings	Only provides age in 5-year categories, rather than allowing for calculation of an actual age.

			before or after a hospital episode of care.	
Monitoring of ongoing medication use	N/A	No	Yes, possible via linkage to PBS	Expected duration of supply may be unknown

1.5.2 Aims and Objectives

This PhD project will provide insights into two key areas. Firstly, it will elucidate current AHA prescribing patterns and the extent to which age, sex, comorbidities and other demographic factors are associated with the prescribing of different T2D treatments in Australia. This will be achieved using the 10% Random Sample of the Pharmaceutical Benefits Scheme (PBS) data and the National Diabetes Services Scheme (NDSS) dataset linked to PBS dispensings. The second area of study will address AHA prescribing and clinical outcomes associated with AHAs in hospital settings. The Eastern Health (EH) Dataset and the Victorian Admitted Episodes Dataset (VAED) linked to PBS dispensings will be used to meet this objective.

The specific aims of this PhD project are:

1. To determine the patterns and predictors of pharmacological treatment initiation for T2D and whether treatment initiation is consistent with Australian clinical practice guidelines that recommend metformin monotherapy (Chapter 2).
2. To estimate factors that predict switching and addition of AHAs in the year after initiating metformin or a sulfonylurea for T2D (Chapter 3).
3. To determine whether age, frailty, or dementia predict discharge treatment types for patients with T2D and related complications (Chapter 4).
4. To determine whether SGLT-2Is, compared to DPP-4Is, prevent MACE, HHF and mortality in frail people with type 2 diabetes (Chapter 5).

The overall objective of this PhD is to inform clinical practice about the quality use of medicines in people with T2D and to contribute to ongoing surveillance of current medical practice in the pharmacological treatment of T2D.

Chapter 2: Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?

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Research: Epidemiology

Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?

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What's new?

- Metformin or sulfonylurea monotherapy are guideline recommended initial treatments for type 2 diabetes in Australia.
- Some 86% of Australians with type 2 diabetes received metformin monotherapy, 5% sulfonylurea monotherapy, 2% other monotherapy and 8% combination therapy as initial pharmacotherapy.
- Initial sulfonylurea monotherapy prescribing has become less frequent in recent years.
- People initiating combination therapy were more likely to be men and to have fewer comorbidities.
- Prescribing patterns for type 2 diabetes medications in Australia indicate a high level of concordance with clinical practice guidelines.

Abstract

Aim To determine the patterns and predictors of pharmacological treatment initiation for type 2 diabetes and whether treatment initiation is consistent with Australian clinical practice guidelines that recommend metformin monotherapy.

Methods Individuals aged 40–99 years initiating a non-insulin type 2 diabetes medication between July 2013 and February 2018 were identified from a 10% random national sample of pharmacy dispensing data. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the predictors of initiating sulfonylurea monotherapy, non-guideline monotherapy and combination therapy compared with metformin monotherapy. Predictors included age, sex, initiation year and comorbidities determined using the Rx-Risk comorbidity index.

Results Of the 47 860 initiators, [47% women, mean age 60.7 (SD 12.1) years], 85.8%, 4.6%, 1.9% and 7.7% received metformin monotherapy, sulfonylurea monotherapy, non-guideline monotherapy and combination therapy, respectively. Increasing age was associated with increasing odds of initiating sulfonylurea monotherapy and non-guideline monotherapy. Combination therapy initiation was less likely in women (OR 0.74, 95% CI 0.69–0.79) and people with more comorbidities (e.g. OR 0.36, 95%

CI 0.29–0.44 for seven or more comorbidities vs. no comorbidities) but more likely in congestive heart failure (OR 1.42, 95% CI 1.22–1.65), cerebrovascular disease (OR 1.50, 95% CI 1.32–1.69) and dyslipidaemia (OR 1.29, 95% CI 1.19–1.40).

Conclusion Treatment initiation in Australia is largely consistent with clinical practice guidelines, with 86% of individuals initiating metformin monotherapy. Initiation on combination therapy was more common in men and in those with fewer comorbidities.

Introduction

In recent years, there has been a rapid increase in the use and cost of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium– glucose cotransporter-2 (SGLT-2) inhibitors and glucagon like peptide-1 (GLP-1) agonists [1]. Currently, it is unclear to what extent these treatments are prescribed, either alone or in combination with other anti-hyperglycaemic agents, as initial treatment for type 2 diabetes. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) advise that dual therapy should be initiated if HbA_{1c} > 58 mmol/mol (7.5%) [2,3], whereas the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advise that treatment should be initiated with two type 2 diabetes medications concurrently if HbA_{1c} ≥ 75 mmol/mol (9.0%) [4]. Conversely, Australia's general practice guidelines and Therapeutic Guidelines (TG) make no recommendations about initiating treatment with combination antihyperglycaemic agents, regardless of HbA_{1c} levels [5,6]. Australian guidelines also recommend that patients initially trial either metformin or sulfonylurea monotherapy, with progression to other type 2 diabetes therapies reserved for those who cannot tolerate or do not respond sufficiently to initial therapy [5,6].

Metformin monotherapy is generally preferred as first-line treatment because it is cost-effective and does not cause hypoglycaemia or weight gain [5]. It is associated with lower cardiovascular mortality when compared with sulfonylureas and may reduce the risk of myocardial infarction, stroke, and atrial fibrillation [7]. One reason for not initiating treatment with metformin is concern over metformin-induced lactic acidosis. Meta-analyses have demonstrated that metformin is not associated with substantially increased lactate concentrations in people with mild-to-moderate chronic kidney disease but acknowledge there is insufficient evidence in severe chronic kidney disease [8]. In 2016, the US Food and Drug Administration (FDA) revised the product information to contraindicate metformin prescribing in patients with estimated glomerular filtration rate (eGFR) < 30 ml min 1.73 m^2, whereas it was previously also contraindicated in mild and moderate renal impairment [9]. Both metformin and sulfonylureas are reimbursed as initial treatment through Australia's Pharmaceutical Benefits Scheme (PBS), with sulfonylureas an option when metformin is contraindicated or poorly tolerated [5]. Other classes of medications such as thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists are not considered first-line. To attract government reimbursement for patients prescribed these medications, prescribers are required to confirm that either metformin or a sulfonylurea has been used and was either not tolerated or not sufficient to allow the patient to reach their glycaemic target.

In Australia, metformin-containing fixed-dose combination products with sulfonylureas, thiazolidinediones, DPP-4 inhibitors and SGLT-2 inhibitors are available. Up to 22% of metformin–glibenclamide initiations among Australian veterans were in people with no history of using either component [10]. Expert opinion in Australia and internationally is divided on whether treatment should always be initiated with metformin monotherapy in people presenting with poor glycaemic control. This is because it is unclear whether the advantages of early, aggressive treatment are outweighed by higher costs and possible adverse events [11]. No previous studies have investigated the patterns of treatment initiation for type 2 diabetes in the general Australian population. The

objective of this study is to determine the patterns and predictors of treatment initiation for type 2 diabetes in Australia and whether treatment initiation is consistent with current clinical practice guidelines.

Participants and methods

Study design, data source and study population

We conducted a population-based study on predictors of type 2 diabetes medication initiation between July 2013 and February 2018. We utilized data from a 10% simple random sample of Australia's PBS. These data are considered nationally representative of dispensing for all Australia's 25 million population and have been widely used in drug utilization research [12].

Under the PBS, Australian citizens, permanent residents and people from countries with reciprocal healthcare agreements are entitled to receive a broad range of government subsidized medications. The data contain information about each dispensed medication's PBS item code, strength, dispensed quantity, date of prescribing and date of supply. The data also contain information on the recipients' year of birth, sex, year of death and concessional status.

The study population included adults aged between 40 and 99 years who had been dispensed a non-insulin medication for type 2 diabetes between 1 July 2013 and 28 February 2018. The former date was chosen because the 10% PBS sample does not contain records for medications priced below co-payments prior to 1 July 2012. All people who initiated with insulin were excluded because we could not exclude the possibility that these people had type 1 diabetes. We also excluded individuals under 40 years to minimize the number of people in our data who were prescribed metformin for polycystic ovarian syndrome. A study from the United Kingdom showed that the incidence rate ratio (IRR) for metformin prescribing in women with polycystic ovarian syndrome is very low in the 40–44 vs. 20– 24 years age group [IRR 0.17, 95% confidence intervals (CI)
0.16–0.18] [13].

Measures and definitions

Medication initiation for type 2 diabetes was defined as the first dispensing (index date) of a medication with Anatomical Therapeutic Chemical (ATC) code A10B between 1 July 2013 and 28 February 2018 and no record of anti-diabetic medication (ATC code A10) dispensing during one year prior to the index date. Type 2 diabetes medications at initiation were classified as: (1) metformin monotherapy (A10BA); (2) sulfonylurea monotherapy (A10BB); (3) non-guideline monotherapy, acarbose (A10BF), thiazolidinediones (A10BG), DPP-4 inhibitors (A10BH), GLP-1 agonists (A10BJ) or SGLT-2 inhibitors (A10BK and A10BX), and 3) combination therapy (A10BD) and when people were dispensed more than one individual type 2 diabetes medication on their index date.

The Rx-Risk Index (Appendix S1), was used to identify each person's comorbidities by using medication dispensing during the year prior to the index date as a proxy for comorbidities. This index has been validated for use with Australian PBS data and permits a comorbidity score for an individual to be calculated [14]. In addition to the comorbidity score, individual comorbidities considered to be important predictors of initial type 2 diabetes treatment were considered separately. These included atrial fibrillation, cerebrovascular disease, congestive heart failure, depression, dyslipidaemia, hypertension, ischemic heart disease/angina and ischemic heart disease/hypertension. End stage renal disease was not included in the multivariate analysis because the number of individuals in this category was too low. We considered cardiovascular comorbidities because the Australian guidelines advise consideration of cardiovascular disease when selecting a type 2 diabetes medication and recommend that metformin should be used with caution in people

with cardiac disease [5]. An individual comorbidity was included in the final model if the unadjusted P-value associated with the odds ratio (OR) was < 0.1.

Statistical analysis

Baseline characteristics were presented as means with standard deviations (SD) or as a frequency and percentage. Predictors of treatment initiation were estimated using multinomial logistic regression. Adjusted ORs and 95% CI were estimated for predictors of sulfonylurea monotherapy, non-guideline monotherapy and combination therapy compared with metformin monotherapy. All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Monash University Human Research Ethics Committee. The study protocol and final manuscript was approved by Australian Government Department of Human Services.

Results

Cohort characteristics

Of the 47 860 people who initiated type 2 diabetes medications, 85.8% initiated metformin monotherapy, 4.6% sulfonylurea monotherapy, 1.9% non-guideline monotherapy and 7.7% combination therapy. The mean age at the time of medication initiation was 60.7 (12.1) years (Table 1). The mean ages of people initiating metformin monotherapy, sulfonylurea monotherapy, non-guideline monotherapy and combination therapy were 60.3 (11.8), 67.7 (13.3), 65.1 (12.5) and 60.1 (12.1) years, respectively.

Women accounted for 47.8% of those initiating metformin monotherapy, 45.4% of sulfonylurea monotherapy, 47.5% of non-guideline monotherapy and 38.2% of combination therapy. In the group initiating non-guideline monotherapy, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists were dispensed to 52.0%, 21.5% and 12.3% of individuals, respectively. Characteristics of people prescribed each class of non-guideline monotherapy are provided (Appendix S2) but were not included in the multinomial logistic analysis due to insufficient numbers. Gliclazide constituted 87% of all sulfonylurea monotherapy initiations. Of those who initiated a combination therapy, 54% initiated a fixed-dose combination product and 97% were combinations with metformin. Of the combination therapy initiators, 92.3% initiated with two medications, 7.2% with three medications and 0.6% with more than three medications.

The mean (SD) number of estimated comorbidities in the metformin monotherapy, sulfonylurea monotherapy, nonguideline monotherapy and combination therapy groups were 3.9 (2.5), 4.9 (3.0), 4.4 (2.9) and 3.6 (2.6), respectively.

Predictors on type 2 diabetes treatment initiation

There was a graded association between age and odds of initiating with either non-guideline monotherapy or sulfonylurea monotherapy, with people aged ≥ 80 years compared with those aged 40–49 years having more than three times the odds of initiating a non-guideline monotherapy (OR 3.37, 95% CI 2.56–4.43) and almost five times the odds of initiating sulfonylurea monotherapy (OR 4.95, 95% CI 4.15–5.91) (Table 2). The association between age and initiating combination therapy, however, was less clear. Women were less likely than men to initiate combination therapy (OR 0.74, 95% CI 0.69–0.79).

Compared with people with no comorbidities, people with one to three comorbidities (OR 0.56, 95% CI 0.49–0.64), four to six comorbidities (0.39, 95% CI 0.33–0.45) and seven or more comorbidities (0.36, 95% CI 0.29–0.44) had lower odds of receiving combination therapy.

Congestive heart failure (OR 1.59, 95% CI 1.37–1.83), atrial fibrillation (OR 1.30, 95% CI 1.13–1.50) and cerebrovascular disease (OR 1.29, 95% CI 1.13-1.47) were associated with higher odds of initiating sulfonylurea monotherapy.

Congestive heart failure (OR 1.42, 95% CI 1.22–1.65), cerebrovascular disease (OR 1.50, 95% CI 1.32–1.69) and dyslipidaemia (OR 1.29, 95% CI 1.19–1.40) were associated with higher odds of initiating combination therapy. Depression was associated with lower odds of initiating sulfonylurea monotherapy (OR 0.81, 95% CI 0.72–0.91) and combination therapy (OR 0.86, 95% CI 0.78–0.95). Dyslipidaemia was associated with lower odds of initiating sulfonylurea monotherapy (OR 0.84, 95% CI 0.76–0.93) and non-guideline monotherapy (OR 0.83, 95% CI 0.71–0.96).

Compared with 2013/2014, the odds of initiating with sulfonylurea monotherapy were lower in 2014/2015 (OR 0.78, 95% CI 0.69–0.88), 2015/2016 (0.69, 95% CI 0.61– 0.78) and 2016/2017 (0.58, 95% CI 0.50–0.66). There was no clear change in the odds of initiating non-guideline monotherapy or combination therapy over the study period.

Table 1 Demographic and clinical characteristics of people by type 2 diabetes medication at treatment initiation

Demographic characteristic	Total (n = 47 860)	Metformin monotherapy (n = 41 060)	Sulfonylurea monotherapy (n = 2212)	Non-guideline monotherapy (n = 917)	Combination therapy (n = 3671)	P-value
Mean age, years	60.7 12.1	60.3 11.8	67.7 13.3	65.1 12.5	60.1 12.1	< 0.0001
Age, years						
40–49	9849 (20.6)	8682 (21.1)	234 (10.6)	120 (13.1)	813 (22.1)	
50–59	13 170 (27.5)	11 521 (28.1)	400 (18.1)	184 (20.1)	1065 (29.0)	
60–69	13 371 (27.9)	11 552 (28.1)	555 (25.1)	271 (29.6)	993 (27.0)	
70–79	8045 (16.8)	6751 (16.4)	548 (24.8)	214 (23.3)	532 (14.5)	
80+	3425 (7.2)	2554 (6.2)	475 (21.5)	128 (14.0)	268 (7.3)	< 0.0001
Sex, female	22 475 (47.0)	19 632 (47.8)	1004 (45.4)	436 (47.5)	1403 (38.2)	< 0.0001
Index year						
7/2013 to 6/2014	11 504 (24.0)	9671 (23.6)	713 (32.2)	198 (21.6)	922 (25.1)	
7/2014 to 6/2015	10 438 (21.8)	8950 (21.8)	519 (23.5)	157 (17.1)	812 (22.1)	
7/2015 to 6/2016	9641 (20.1)	8319 (20.3)	423 (19.1)	207 (22.6)	692 (18.9)	
7/2016 to 6/2017	9917 (20.7)	8580 (20.9)	361 (16.3)	202 (22.0)	774 (21.1)	
7/2017 to 2/2018*	6360 (13.3)	5540 (13.5)	196 (8.9)	153 (16.7)	471 (12.8)	<0.0001
Mean comorbidity score	3.9 2.5	3.9 2.5	4.9 3.0	4.4 2.9	3.6 2.6	< 0.0001
Number of comorbidities†						
0	2685 (5.6)	2165 (5.3)	109 (4.9)	71 (7.7)	340 (9.3)	
1–3	20 923 (43.7)	18 171 (44.3)	692 (31.3)	321 (35.0)	1739 (47.4)	
4–6	16 657 (34.8)	14 545 (35.4)	735 (33.2)	295 (32.2)	1082 (29.5)	
7+	7595 (15.9)	6179 (15.0)	676 (30.6)	230 (25.1)	510 (13.9)	< 0.0001
Atrial fibrillation	3589 (7.5)	2879 (7.0)	349 (15.8)	105 (11.5)	256 (7.0)	< 0.0001
Cerebrovascular disease	4719 (9.9)	3737 (9.1)	415 (18.8)	124 (13.5)	443 (12.1)	< 0.0001
Congestive heart failure	2924 (6.1)	2250 (5.5)	331 (15.0)	83 (9.1)	260 (7.1)	< 0.0001
Depression	11 047 (23.1)	9669 (23.5)	502 (22.7)	229 (25.0)	647 (17.6)	< 0.0001
Dyslipidaemia	23 135 (48.3)	19 638 (47.8)	1197 (54.1)	451 (49.2)	1849 (50.4)	< 0.0001
End stage renal disease	126 (0.3)	26 (0.1)	85 (3.8)	9 (1.0)	6 (0.2)	< 0.0001
Hypertension	23 081 (48.2)	19 694 (48.0)	1239 (56.0)	464 (50.6)	1684 (45.9)	< 0.0001
Ischaemic heart disease/angina	2136 (4.5)	1727 (4.2)	198 (9.0)	54 (5.9)	157 (4.3)	< 0.0001
Ischaemic heart disease/hypertension	14 692 (30.7)	12 419 (30.2)	872 (39.4)	317 (34.6)	1084 (29.5)	< 0.0001

*Data were recorded until the end of February 2018, therefore the final index year is incomplete with respect to number of initiations.
†A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had type 2 diabetes medications prescribed at baseline.

Table 2 Predictors of initiation on different type 2 diabetes therapies, among those initiating a non-insulin type 2 diabetes medication

Demographic characteristic	Sulfonylurea monotherapy (n = 2212)		Non-guideline monotherapy (n = 917)		Combination therapy (n = 3671)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age, years						
40–49	1.00	Reference	1.00	Reference	1.00	Reference
50–59	1.26	1.07–1.49	1.20	0.95–1.51	0.96	0.88–1.06
60–69	1.65	1.41–1.94	1.78	1.42–2.23	0.89	0.80–0.98
70–79	2.53	2.14–2.99	2.30	1.81–2.94	0.82	0.73–0.93
80+	4.95	4.15–5.91	3.37	2.56–4.43	1.10	0.94–1.28
Sex, female	0.93	0.85–1.02	1.00	0.87–1.14	0.74	0.69–0.79
Index year						
7/2013 to 6/2014	1.00	Reference	1.00	Reference	1.00	Reference
7/2014 to 6/2015	0.78	0.69–0.88	0.85	0.69–1.05	0.96	0.87–1.06
7/2015 to 6/2016	0.69	0.61–0.78	1.21	0.99–1.47	0.89	0.80–0.98
7/2016 to 6/2017	0.58	0.50–0.66	1.15	0.94–1.41	0.97	0.88–1.07
7/2017 to 2/2018*	0.48	0.41–0.57	1.35	1.09–1.67	0.92	0.82–1.03
Number of comorbidities†						
0	1.00	Reference	1.00	Reference	1.00	Reference
1–3	0.74	0.60–0.92	0.55	0.42–0.72	0.56	0.49–0.64
4–6	0.79	0.62–1.00	0.57	0.41–0.77	0.39	0.33–0.45
7+	1.21	0.92–1.59	0.90	0.62–1.32	0.36	0.29–0.44
Atrial fibrillation	1.30	1.13–1.50	1.12	0.89–1.42	1.09	0.94–1.26
Cerebrovascular disease	1.29	1.13–1.47	1.19	0.96–1.49	1.50	1.32–1.69
Congestive heart failure	1.59	1.37–1.83	1.08	0.84–1.40	1.42	1.22–1.65
Depression	0.81	0.72–0.91	0.97	0.82–1.16	0.86	0.78–0.95
Dyslipidaemia	0.84	0.76–0.93	0.83	0.71–0.96	1.29	1.19–1.40
Hypertension	1.03	0.94–1.14	0.94	0.81–1.09	1.05	0.97–1.14
Ischaemic heart disease/angina	1.02	0.86–1.22	0.89	0.65–1.20	0.86	0.71–1.03
Ischaemic heart disease/hypertension	0.99	0.90–1.10	0.95	0.81–1.11	1.08	0.99–1.18

CI, confidence interval; OR, adjusted odds ratio.
*Data were recorded until the end of February 2018, therefore the final index year is incomplete with respect to number of initiations.
†A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had type 2 diabetes medications prescribed at baseline.

Discussion

The main finding of our study was that 86% of people initiate treatment with metformin, suggesting a high concordance with clinical practice guidelines. This is consistent with metformin having established long-term safety, favourable adverse event profile and low risk of weight gain or hypoglycaemia [5]. The result is also likely to reflect prescribers' familiarity with this medication because it has been the first-line treatment for type 2 diabetes for many years in Australia.

The decreasing odds of initiating with sulfonylurea monotherapy over time is consistent with research by Wilkinson et al. [15] that reports decreased sulfonylurea prescribing in the UK in recent years. Among those who initiated sulfonylureas, gliclazide constituted 87% of initiations. This may be because gliclazide is specifically listed in the Australian diabetes general practice guidelines as being the only sulfonylurea that does not increase cardiovascular risk when used as monotherapy compared with metformin [5]. It is also likely to reflect longstanding prescriber familiarity with this medication. There was no apparent trend in the initial prescribing of non-guideline monotherapies, although it is known to be increasing overall [1]. Data in Appendix S2 indicate that initial prescribing of SGLT-2 inhibitors is increasing, possibly demonstrating prescribers' increasing familiarity with the robust benefits of this class in preventing hospitalizations for heart failure and progression of renal disease [17].

In our study, older individuals were more likely to initiate non-guideline monotherapy and sulfonylurea monotherapy than were younger individuals. This may be explained by the higher prevalence of renal impairment in older people [18]. It may also reflect that Australian guidelines

include ‘cardiac disease’ as a precaution for prescribing metformin and cardiac disease is more prevalent in older people [5]. The guideline recommendation is at odds with recent systematic reviews that have demonstrated metformin is associated with reduced all-cause mortality and with a lower risk of chronic heart failure readmission in people with chronic heart failure [19]. Conversely, other anti-hyperglycaemic agents, such as insulin, sulfonylureas and thiazolidinediones are associated with increased risk of mortality in patients with existing chronic heart failure [20]. There is uncertainty over the clinical and economic outcomes associated with initiating multiple type 2 diabetes medications concurrently rather than sequentially [21], although the latter approach is advised in Australian guidelines [5,6]. Further studies are required to provide evidence for which approach is superior [22]. It has been hypothesized that using medications with complementary mechanisms of action at treatment initiation in type 2 diabetes could delay disease progression [23].

The ADA/EASD recommend initiating dual therapy when $HbA_{1c} \geq 75$ mmol/mol (9.0%) but acknowledge the lack of proven advantage with this approach [4]. Similarly, AACE/ACE guidelines state dual therapy is appropriate when $HbA_{1c} > 58$ mmol/mol (7.5%), but the reference cited for this recommendation does not discuss initial combination therapy [2,3]. Australian guidelines do not address the issue [5,6]. Proposed advantages of initiating combination treatment include rapid attainment of glycaemic targets, bypassing of clinical inertia and the preservation of b-cell function [23]. Meta-analyses have shown the relative risk of attaining $HbA_{1c} < 53$ mmol/mol (7.0%) on initial combination therapy vs. initial metformin monotherapy to be 1.4 [24]. A study involving initial treatment with a sitagliptin/metformin fixed-dose combination showed a relative risk of 1.7 for attaining $HbA_{1c} < 48$ mmol/mol (6.5%) [25]. Australian general practice guidelines and the ADA guidelines advise that less stringent HbA_{1c} targets > 53 mmol/mol (> 7.0%) can be considered in people who have ‘important comorbidities’ or ‘established cardiovascular complications’ [4,5]. These guidelines are supported by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which reported that intensive glycaemic control in high-risk patients with advanced atherosclerosis was linked to higher rates of cardiovascular death [26]. In our study, people with a higher number of comorbidities had lower odds of initiating with combination therapy. Compared with people with no comorbidities, people with one to three, four to six and seven or more comorbidities had progressively lower odds of initiating combination therapy. This finding was consistent with Australian general practice recommendations related to less intensive treatment in people with ‘important comorbidities’. Conversely, our study found that chronic heart failure, dyslipidaemia and cerebrovascular disease were positively associated with initiating combination treatment. Because these comorbidities are likely to be indicative of ‘established vascular complications’, this may reflect initial intensive treatment in patients for whom it is not guideline recommended. Finally, our study identified that women were less likely to receive initial combination therapy than men. This may be because women have more regular contact with their general practitioners and thus have less severe type 2 diabetes at the time of diagnosis [27].

Strengths and limitations

We analysed large and representative national data for a 10% random sample of the Australian population. As the Australian government’s PBS provides subsidized access to prescription medications for all Australia’s 25 million citizens, permanent residents and visitors from countries with reciprocal healthcare rights, the pattern of treatment initiation is largely dictated by actual or perceived clinical need rather than a person’s health plan or insurance cover. Our results have implications for other countries that provide universal access to subsidized prescription medications for type 2 diabetes.

These data included records of all reimbursed medications for type 2 diabetes. However, we did not have clinical data such as renal function and HbA_{1c} results, which were likely to have been important

predictors of treatment initiation. Records of in-hospital dispensing are not captured in the data and, therefore, treatment initiation that occurred in hospital was not captured. We reasoned that this would be unlikely to considerably impact our results because most patients would fill prescriptions for the same medications from a community pharmacy following hospital discharge. It is possible that some people initiated with medications other than metformin or sulfonylureas without reimbursement and, therefore, were not included in the PBS data set. However, the number of these people is likely to be small because these medications are relatively expensive. A very small number of people appear to initiate on three or more medications. This may be because they have previously accessed type 2 diabetes medication outside the PBS or in hospital during a long-term stay. The proportion of combination therapy and nonguideline monotherapy initiations may have been underestimated because people dispensed insulin on their index date were not included. However, insulin is rarely prescribed first line treatment in type 2 diabetes [1]. Finally, the number of people commencing metformin monotherapy for type 2 diabetes may have been overestimated because metformin is occasionally used to treat polycystic ovarian syndrome in women over the age of 40 years, although other studies indicate that this number is likely to be very low [13].

Conclusion

Treatment initiation in Australia is largely consistent with clinical practice guidelines, with 86% of individuals initiating metformin monotherapy. Increasing age is associated with an increasing probability of receiving monotherapy other than metformin. Initiation with combination prescribing is more likely to occur in individuals with fewer comorbidities.

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Competing interests

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. RxRisk-V categories

Disease category	Anatomical Therapeutic Classification codes
Atrial Fibrillation (AF)	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05
Cerebrovascular disease	B01AC04-B01AC30
Congestive Heart Failure (CHF)	(C03CA01-C03CC01 AND (C09AA01-C09AA16 OR, C09CA01 - C09CX99)), C03DA04, C07AB07, C07AG02, C07AB12, C09DX04, C07AB02 †
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX26
Diabetes	A10AA01-A10BX08
End Stage Renal Disease (ESRD)	B03XA01-B03XA03, V03AE02, V03AE03, V03AE05
Dyslipidaemia	C10AA01-C10BX12
Hypertension (HT)	C03AA01-C03BA11, C03BB04, C03DA01-C03DA03, C03EA01-C03EA14, C09BA02-C09BA15, C09DA01-C09DA09, C02AB01-C02AC05, C02DB01-C02DB04, C03DB01-C03DB02
Ischaemic Heart Disease (IHD)/Angina	C01DA02-C01DA70, C01DX16, C08EX02
Ischaemic Heart Disease (IHD)/Hypertension (HT)	C07AA01-C07AA06, C07AG01, C08CA01-C08DB01, C09DB01-C09DB08, C09DX01-C09DX03, C09BB02-C09BB12, C07AB03, C07AB02 †

† Metoprolol, (ATC code C07AB02), is used in both CHF and IHD/HT, therefore, PBS item codes were used to identify the indication. PBS codes 8732N, 8733P, 8734Q and 8735R indicated CHF, all other PBS codes for this medication indicated IHD/HT.

Appendix S2. Demographic characteristics of people prescribed initial non-guideline monotherapy for type 2 Diabetes by medication class

Demographic Characteristics	Acarbose N=76	Thiazolidinediones N=54	DPP-4I ‡ N=477	GLP-1A ‡ N=113	SGLT-2I ‡ N=197	P values
Mean age, years	62.6±12.6	65.5±11.3	67.6±12.5	62.2±11.9	61.4±11.7	<0.0001
Age, years						
40-49	15 (19.7)	6 (11.1)	43 (9.0)	18 (15.9)	38 (19.3)	
50-59	19 (25.0)	8 (14.8)	88 (18.4)	29 (25.7)	40 (20.3)	
60-69	19 (25.0)	20 (37.0)	118 (24.7)	39 (34.5)	75 (38.1)	
70-79	14 (18.4)	12 (22.2)	138 (28.9)	17 (15.0)	33 (16.8)	
80+	9 (11.8)	8 (14.8)	90 (18.9)	10 (8.8)	11 (5.6)	<0.0001
Sex, female	35 (46.1)	26 (48.1)	237 (49.7)	51 (45.1)	87 (44.2)	0.59
Index year						
7/2013-6/2014	24 (31.6)	24 (44.4)	125 (26.2)	18 (15.9)	7 (3.6)	
7/2014-6/2015	11 (14.5)	12 (22.2)	97 (20.3)	15 (13.3)	22 (11.2)	
7/2015-6/2016	18 (23.7)	7 (13.0)	101 (21.2)	24 (21.2)	57 (28.9)	
7/2016-6/2017	13 (17.1)	9 (16.7)	87 (18.2)	32 (28.3)	61 (31.0)	
7/2017-2/2018*	10 (13.2)	2 (3.7)	67 (14.0)	24 (21.2)	50 (25.4)	<0.0001
Mean comorbidity score	4.2±2.5	4.5±2.8	4.7±3.0	4.1±2.9	4.1±3.0	0.03
Number of comorbidities †						
0	2 (2.6)	3 (5.6)	31 (6.5)	14 (12.4)	21 (10.7)	
1-3	30 (39.5)	20 (37.0)	156 (32.7)	34 (30.1)	81 (41.1)	
4-6	29 (38.2)	17 (31.5)	155 (32.5)	40 (35.4)	54 (27.4)	
7+	15 (19.7)	14 (25.9)	135 (28.3)	25 (22.1)	41 (20.8)	0.0001
Atrial Fibrillation	8 (10.5)	6 (11.1)	61 (12.8)	12 (10.6)	18 (9.1)	0.82
Cerebrovascular Disease	13 (17.1)	10 (18.5)	75 (15.7)	6 (5.3)	20 (10.2)	0.03
Congestive Heart Failure	4 (5.3)	6 (11.1)	51 (10.7)	7 (6.2)	15 (7.6)	0.43
Depression	21 (27.6)	12 (22.2)	107 (22.4)	32 (28.3)	57 (28.9)	0.37
Dyslipidaemia	27 (35.5)	24 (44.4)	261 (54.7)	43 (38.1)	96 (48.7)	0.002
Hypertension	28 (36.8)	31 (57.4)	265 (55.6)	50 (44.2)	90 (45.7)	0.005
Ischaemic Heart disease/Angina	3 (3.9)	2 (3.7)	37 (7.8)	2 (1.8)	10 (5.1)	0.17
Ischaemic Heart Disease /Hypertension	18 (23.7)	20 (37.0)	188 (39.4)	36 (31.9)	55 (27.9)	0.01

†A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had Type 2 diabetes medications prescribed at baseline

‡DPP-4I Dipeptidyl peptidase-4 inhibitor; GLP-1A Glucagon like peptide- 1 agonist; SGLT-2I Sodium glucose cotransporter- 2 inhibitors
* Data were recorded until the end of February, 2018, therefore the final index year is incomplete with respect to number of initiations

2.1 Appendix

The ethics approval number for this study is EO2018/4/468.

Chapter 3: Treatment Dynamics in People who Initiate Metformin or Sulfonylureas for Type 2 Diabetes Mellitus: A Cohort Study

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3.1 Abstract

Aim: To investigate the incidence of, and factors associated with addition and switching of glucose-lowering medications within 12-months of initiating metformin or a sulfonylurea for type 2 diabetes (T2D).

Methods: We identified 109,573 individuals aged 18-99 years who initiated metformin or a sulfonylurea between July 2013 and April 2015 using Australian National Diabetes Service Scheme (NDSS) data linked with national dispensing data. Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CI) for factors associated with time to addition to or switch from metformin or sulfonylurea over a 12-month follow-up.

Results: Treatment addition or switching occurred in 18% and 4% of individuals who initiated metformin and in 28% and 13% of individuals who initiated sulfonylureas. Median time to addition was 104 days for metformin and 82 days for sulfonylureas. Median time to switching was 63 days for metformin and 52 days for sulfonylureas. Congestive heart failure, nicotine dependence, end stage renal disease and dispensing of systemic corticosteroids were associated with higher likelihood of treatment additions and switching in individuals initiating metformin. Antipsychotic dispensing was associated with a higher likelihood of treatment addition in individuals initiating sulfonylureas. Women initiating metformin were less likely to receive treatment additions but more likely to switch treatment than men.

Conclusion: Nearly one quarter of Australians who initiate treatment for T2D with metformin or sulfonylureas switch or receive additional treatment within 12-months, with those who initiate sulfonylureas more likely to switch or receive additional treatment than those who initiate metformin.

Keywords: Pharmacoepidemiology, glucose-lowering medication, treatment addition, treatment switch

3.2 Introduction

Type 2 diabetes (T2D) is a progressive disease which often requires treatments to be added or switched in order to achieve glycated haemoglobin (HbA_{1C}) targets. Australian guidelines recommend adding a T2D medication when individuals have failed to reach glycaemic targets after 3-6 months of metformin or sulfonylurea monotherapy [1]. Similar treatment recommendations are included in international guidelines [2-3]. Our previous research has demonstrated 90% of Australians initiate medication treatment with either metformin or sulfonylurea monotherapy [4].

People with T2D and other cardiovascular risk factors may benefit from more aggressive treatment for hyperglycaemia [1]. However, the median time to treatment intensification after a high HbA_{1C} reading is greater than one year [5]. Pantalone et al. reported that 44.4% of individuals with an HbA_{1C}≥9.0% (75mmol/mol) did not receive treatment intensification within 6 months [6]. Paul et al. found that delaying treatment intensification beyond one year increases the risk of myocardial infarction (MI), heart failure (HF), stroke and composite cardiovascular events [7].

Early, aggressive treatment is important in younger people due to the elevated risk of premature death from cardiovascular disease (CVD) [8]. However, stringent glycaemic targets in people aged >65 years may increase the risk of hypoglycaemia [9]. People with multimorbidity may be less likely to receive multiple T2D therapies

due to concerns about polypharmacy and drug interactions. T2D medication may be switched due to lack of efficacy or adverse drug events (ADEs). An Irish study reported that sulfonylurea initiators were more likely than metformin initiators to receive a treatment addition or switch within two years [10]. Our study is the first in Australia to distinguish between treatment addition and switching in T2D. The objective of this study was to investigate the incidence of and factors associated with switching and addition of glucose-lowering medications within 12-months of initiating metformin or a sulfonylurea for T2D.

3.3 Materials and methods

3.3.1 Study design, data source and study population

We conducted a national population-based cohort study on the incidence of, and factors associated with T2D medication addition and switching between July 2013 and April 2016. We utilised data from the Australian National Diabetes Services Scheme (NDSS) linked to national pharmacy dispensing data from Australia's Pharmaceutical Benefits Scheme (PBS). Linkage of NDSS and PBS data was performed by the Australian Institute of Health and Welfare (AIHW) for the period of January 2002 to April 2016.

The NDSS provides education and subsidies for 80-90% of Australians diagnosed with diabetes [8]. NDSS registration is performed by a medical practitioner or certified diabetes educator [8]. NDSS data include each registrant's date of birth, date of diabetes diagnosis, postcode and date of death (via a linkage to the National Death Index). Socio-Economic Indexes for Areas (SEIFA) score and Accessibility/Remoteness Index of Australia (ARIA) scores were derived from

postcodes. SEIFA scores were divided into quintiles [11]. The ARIA score identifies five area categories; major urban, inner regional, outer regional, remote, and very remote areas based on distance from major service centres [11]. In our study, the remote and very remote categories (collectively, 2% of the population) were collapsed into one category [11].

The PBS entitles Australia's 25 million citizens, permanent residents and people from countries with reciprocal health care agreements to receive government-subsidised medications. PBS data include medication name and strength, dispensed quantity, date of prescribing and date of supply. PBS reimbursement criteria require people to trial metformin or a sulfonylurea before other T2D medications.

The study population included all adults aged 18 to 99 years diagnosed with T2D who initiated metformin or a sulfonylurea (the index medication) between July 1, 2013, and April 30, 2015. The index date was the date of first dispensing of either metformin or sulfonylurea with no dispensings of any diabetes medications in the previous 12 months (Figure 1). We excluded individuals dispensed more than one T2D medication on their index date or with a recorded date of death on or prior to their index date.

3.3.2 Measures and definitions

Metformin (A10BA) and sulfonylureas (A10BB) were categorised using the Anatomical Therapeutic Chemical (ATC) classification system [12]. Sulfonylureas included glibenclamide, gliclazide, glimepiride and glipizide.

The Rx-Risk Index was used to identify each person's comorbidities based on medication dispensing. The index has been validated for use with Australian PBS data [13]. All people had T2D, so we deducted 1 from each individual's comorbidity score. We also used the Rx-Risk Index to infer specific comorbidities during the year prior to the index date. These comorbidities included congestive heart failure (CHF), hyperlipidaemia, depression, nicotine dependence, hypertension, and end stage renal disease (Appendix A). Depression is known to be associated with poor adherence [14] and tobacco smoking with cardiovascular risk [15]. Dispensings of systemic corticosteroids (ATC code H02A) or antipsychotics (N05A) in the 3 months prior to the index date were included in the model because these medications may affect glycaemic control. Other potential factors we investigated were age, socioeconomic status (SEIFA), remoteness/rurality (ARIA), sex, Aboriginal or Torres Strait Islander status and time between T2D diagnosis and the index date. The date of diabetes diagnosis was missing for 16% of individuals and for these individuals we used the date of the NDSS enrolment as a proxy for date of diagnosis.

3.3.3 Outcome measures

Medication addition or switching was defined as dispensing of a T2D medication other than the index medication, including metformin, sulfonylurea, acarbose (A10BF), thiazolidinedione (A10BG), dipeptidyl peptidase-IV inhibitor (DPP-4I; A10BH) glucagon-like peptide-1 agonist (GLP-1A; A10BJ), sodium-glucose cotransporter-2 inhibitor (SGLT-2Is; A10BK and A10BX), fixed dose combination therapy (A10BD) or insulin (A10A). Insulins included all available insulin products (fast acting, intermediate acting long acting and mixed insulin and insulin analogues for injection or inhalation) [12].

The duration of each prescription was estimated using the prescription refill period. The duration of a specific PBS medication was defined as the period in which 75% of the population refilled their prescription for that item [16]. If an individual did not refill the index medication before the end of the grace period for the previous supply, the individual was deemed to have discontinued the index medication. An addition was defined as dispensing of a new T2D medication without discontinuing the index medication. A switch was defined as dispensing of a new T2D medication after the last dispensing of a discontinued index medication (Figure 2). When investigating additions of medications, people were censored on the date of switching, death date or 1 year after their index date, whichever occurred first. When investigating switching of medications, people were censored on the date of addition, death date or 1 year after their index date, whichever occurred first.

3.3.4 Statistical analysis

Baseline characteristics of the study cohorts were presented as means with standard deviations (SD), medians with interquartile ranges (IQR) or as a frequencies and percentages. All analyses were conducted separately for people who initiated metformin and sulfonylurea. The proportional hazards assumption was confirmed, and Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CI) for factors associated with time to switching from or addition to initial monotherapy within 365 days. HRs were estimated for age, comorbidity score, SEIFA score, ARIA score, CHF, hyperlipidaemia, depression, nicotine dependence, hypertension, end stage renal

disease and the dispensing of antipsychotics or systemic corticosteroids during the previous 3 months.

Sensitivity analyses were performed using different grace periods to define index medication continuation or discontinuation using similar methods to a study by Caughey et al. [14]. We also conducted sensitivity analysis excluding individuals dispensed antipsychotics or systemic corticosteroids during the three months prior to the index date to determine if the inclusion of individuals with possible drug-induced T2D may have biased the results towards more aggressive treatment. A third sensitivity analysis (Appendix B) was conducted for individuals dispensed >80% of their prescriptions while eligible for higher PBS reimbursement (concession beneficiaries). Our data was more complete for concession beneficiaries prior to July 2012 and so this provided the opportunity to utilise a two-year lookback period to verify our main analysis successfully captured incident users. All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Monash University Human Research Ethics Committee.

3.4 Results

3.4.1 Cohort characteristics

Of the 109,573 people in the study cohort, 93.8% initiated metformin and 6.2% initiated a sulfonylurea. The mean ages of people initiating metformin and sulfonylurea therapy were 58.7 (SD 13.2) and 65.7 (SD 14.6) years, respectively, (Table 1). Of the metformin and sulfonylurea initiators, 44.4% and 44.2%, respectively, were women. The respective median numbers of comorbidities in the

metformin and sulfonylurea cohorts were 3 (IQR 2—5) and 4 (IQR 2—7). The median time until initiation of the index medication after diagnosis of T2D was 0.2 (IQR 0.0-4.7) years in the metformin initiators and 4.4 (IQR 0.1-9.9) years among sulfonylurea initiators.

3.4.2 Incidence of an addition or switch

For metformin initiators, the proportions of individuals receiving an addition or switch during the first year were 18% and 4%, respectively, whereas among sulfonylurea initiators the proportions were 28% and 13%, respectively. Overall, 23.2% of the cohort received an addition or a switch. The median time to addition amongst those individuals who received one was 104 days in the metformin cohort and 82 days in the sulfonylurea cohort. The median time to switching amongst those individuals who received one was 63 days in the metformin cohort and 52 days in the sulfonylurea cohort.

3.4.3 Factors associated with T2D treatment addition or switch

In both cohorts, there was an inverse association between age and the risk of receiving add-on therapy. In the metformin cohort, compared to people aged 18-49 years, people aged 50-74 (HR 0.77; 95%CI 0.75—0.80) and 75-99 (HR 0.57; 95%CI 0.54—0.61) had lower risks of receiving additions. In the sulfonylurea cohort, compared to people aged 18-49 years, people aged 50-74 (HR 0.70; 95%CI 0.62—0.79) and 75-99 (HR 0.44; 95%CI 0.38—0.52) also had lower risks of receiving add-on therapy, (Table 2). Sulfonylurea initiators aged 50-74 (HR 0.69; 95%CI 0.58—0.82) and 75-99 years (HR 0.42; 95%CI 0.33—0.54) had a lower risk of switching compared with initiators aged 18-49 years.

Compared with men, women commencing metformin were less likely to receive an add-on medication (HR 0.84; 95%CI 0.81—0.86), but more likely to have their metformin switched (HR 1.42; 95%CI 1.33—1.51). Switching from metformin was also more likely in people with ≥5 (HR 1.40; 95%CI 1.18—1.66) comorbidities compared to those without comorbidities. Sulfonylurea initiators with ≥5 (HR 0.68; 95%CI 0.49—0.96) comorbidities had lower risks of switching compared to those without comorbidities.

In the metformin cohort, CHF (HR 1.29; 95% CI 1.21—1.38), nicotine dependence, (HR 1.31; 95% CI 1.22—1.42), depression (HR 1.09; 95% CI 1.05—1.13), systemic corticosteroids (HR 1.15; 95% CI 1.08—1.22), antipsychotics (HR 1.21; 95% CI 1.13—1.31) and end stage renal disease (HR 1.91; 95% CI 1.23—2.97), were associated with a higher likelihood of receiving add-on therapy. CHF (HR 1.27; 95% CI 1.12—1.44), nicotine dependence, (HR 1.26; 95% CI 1.07—1.48), systemic corticosteroids (HR 1.47; 95% CI 1.32—1.64) and end stage renal disease (HR 2.39; 95% CI 1.19—4.79), were associated with switching from metformin. People initiating metformin who were dispensed lipid-lowering medications were less likely to receive additions (HR 0.87; 95% CI 0.84—0.90), or to switch (HR 0.81; 95% CI 0.75—0.87). In the sulfonylurea cohort, CHF (HR 1.23; 95% CI 1.06—1.44) and antipsychotics (HR 1.60; 95% CI 1.27—2.03) were associated with receiving additional therapy.

Metformin initiators had progressively lower risks of receiving additions to their index medication as time between T2D diagnosis and index date increased from 0-1 year

(HR 0.86; 95% CI 0.83—0.89) to 1-2 years (HR 0.77; 95% CI 0.71—0.82) compared to people who received index medication on their T2D diagnosis date. Sulfonylurea initiators with 0-1 year (HR 0.80; 95% CI 0.69—0.92), and 1-2 years (HR 0.54; 95% CI 0.43—0.69) between their T2D diagnosis and index date also had lower risks or receiving additional therapy compared to people who received index medication on their T2D diagnosis date.

3.4.4 Medications added or switched to

The medications most frequently added to metformin were DPP-4Is (48.5%), sulfonylureas (33.0%) and insulin (11.0%), (Table 3). The medications most frequently added to sulfonylureas were metformin (62.7%), DPP-4Is (13.3%), and insulin (12.5%). People who switched from metformin were most likely to switch to sulfonylureas (61.6%), insulin (17.6%) or DPP-4Is (15.2%) whereas people switching from a sulfonylurea were most likely to switch to metformin (58.5%), insulin (20.4%) or DPP-4Is (10.4%).

3.4.5 Sensitivity analyses

In the first sensitivity analysis, a small number of people (0.7% of people in the metformin cohort and 0.9% of the sulfonylurea cohort), were reclassified as having received add-on therapy where they were previously classified as having switched; however, it did not result in any significant changes to our results in the multivariate models. There were also no substantial changes to our results when we excluded people who received antipsychotic medication or systemic corticosteroids during the three months prior to their index date. Appendix B shows the results obtained when we repeated the analysis in a concessional population with a two-year lookback

period, which were generally similar to the main analysis but contained wider confidence intervals due to the smaller population size.

3.5 Discussion

The main finding of this national study was 23.2% of individuals who initiated metformin or a sulfonylurea either switched or received additional treatment within 12-months. Our results were similar to those of an Irish study which reported 35% of metformin and sulfonylurea initiators changed regimens within two years [10]. Our results also showed that people who initiated sulfonylureas were more likely to switch or receive additional treatment than those who initiate metformin.

Higher rates of treatment switching and addition in people who initiate sulfonylureas may reflect poorer glycaemic control or a higher incidence of ADEs [17]. Although sulfonylureas lower blood glucose to a greater extent than metformin, both metformin and sulfonylureas have similar effectiveness in achieving target HbA_{1C} [18]. However, sulfonylureas have a less favourable ADE profile including weight gain and the risk of hypoglycaemia [18]. Current Australian and international guidelines recommend SGLT-2Is and GLP-1As in preference to sulfonylurea monotherapy in people with heart failure or chronic renal disease [1,2]. However, this recommendation was not included in the 2014–15 guidelines [19]. For this reason, the higher rates of treatment additions and switches in those who initiated sulfonylureas were unlikely to be explained by prescriber adherence to clinical practice guidelines.

Older people who initiated sulfonylureas were less likely to switch than younger people. Older people have a higher prevalence of renal impairment and therefore, few other glucose-lowering medication alternatives. International guidelines [1,2,19,20] state that SGLT-2Is and the GLP-1A exenatide are contraindicated in individuals with a creatinine clearance <30ml/min/1.73m^2. It is recommended that metformin be used with caution in people with mild to moderate renal impairment [21]. This may have contributed to a lower rate of metformin initiation and to clinical inertia. In 2016 US Food and Drug Administration (FDA) advised that metformin is safe to use in people with mild to moderate renal impairment, acknowledging that the risk of lactic acidosis had been overstated [21]. Older age was associated with longer time to addition in both sulfonylurea and metformin initiators, possibly reflecting more conservative prescribing for older adults in whom stringent glycaemic control is not recommended [1,9]. Chronic kidney disease is more common in people with multimorbidity [22]. This may explain why metformin initiators with 5 or more comorbidities had a 40% higher risk of switching compared to those without comorbidities. Moreover, metformin initiators with end stage renal disease had 2.4 times the risk of switching, compared to those without it.

Longer time to treatment switching and addition was observed among people dispensed lipid-lowering medications. A higher proportion of these individuals may have had cardiovascular disease in whom HbA_{1C} targets are likely to be less stringent [1]. Another explanation is that these people had poor glycaemic control linked to statins [23]. However, statin use has only been associated with modest glycaemic changes [24]. Conversely, people with CHF had a higher risk of receiving add-on therapy. This may be because co-existing T2D and CHF are associated with

increased mortality compared to either condition alone [25] and a 25% increased risk of cardiovascular death or heart failure hospitalization after 34 months for every 1% increase in HbA_{1C} level [26]. Smoking cessation attempts were associated with receiving add-on therapy and switching. A cohort study by Lycett et al. found smoking cessation was independently associated with deterioration in glycaemic control lasting for three years [27]. This may explain the higher rate of addition and switching among individuals dispensed smoking cessation products. It may also reflect more intensive diabetes management in people who smoke.

Time between diabetes diagnosis and treatment initiation was associated with treatment addition. Compared to individuals dispensed their index T2D medication on their diagnosis date, people with time intervals <1 year and between 1-2 years had progressively longer times to index medication add-ons. People with less severe diabetes may take longer to initiate their first therapy, and longer to get to their second. Clinical inertia, which refers to healthcare providers not initiating or intensifying therapy when indicated [28] could be a secondary explanation, as prescribers who are slow to prescribe initial therapy are likely to be slow to initiate further therapies. Potential contributors to clinical inertia include resistance to prescribing new medications and concerns about medication costs [29]. There are disadvantages of delaying treatment addition. Desai et al. found people taking metformin or a sulfonylurea with HbA_{1C} ≥7.0% (53mmol/mol), who received an additional T2D therapy between 1-2 years were 22% less likely to achieve target glycaemic levels during the 7 year follow up compared with those who received one within 12 months [30]. Finally, the median time between diagnosis and treatment initiation was longer for people initiating a sulfonylurea than metformin. Sulfonylurea

initiators were older than metformin initiators and so this is consistent with a study by Zhang et al. who found that time to glucose-lowering medication initiation after T2D diagnosis was significantly longer for people aged ≥65 years than for those aged under 65 years [31].

3.5.1 Strengths and limitations

Our study has several important strengths. Firstly, the NDSS data were nationally representative and included 80-90% of all people with T2D in Australia [8]. Secondly, the data were linked to individual level dispensing data. Thirdly, this was the first study from Australia to investigate factors associated with treatment additions and switching. However, NDSS data were incomplete regarding clinical variables such as body mass index, smoking status, renal function or HbA_{1C}. NDSS does not include information on ADEs of diabetes medications. We lacked comprehensive information on all patient demographics, lifestyle factors, co-morbid conditions and genetic factors. Genetic factors may modify the effect of sulfonylureas and thiazolidinediones which could, therefore, be associated with switching and addition [32]. It is possible that add-ons were misclassified as switches if individuals were non-adherent to their index medication. However, our sensitivity analysis, which used longer grace periods, did not result in substantial changes to our results. Adherence to metformin and sulfonylureas may also be factors affecting the likelihood of add-on and switching. However, individuals with very poor adherence were censored due to apparent discontinuation of the treatment. Finally, we were unable to determine whether individuals used T2D medications as prescribed.

3.5.2 Conclusion

Nearly one quarter of Australians who initiate treatment for T2D with metformin or sulfonylureas switch or receive additional treatment within 12-months, with those who initiate sulfonylureas more likely to switch or receive additional treatment than those who initiate metformin.

3.6 Tables

Table 1. Characteristics of Metformin and Sulfonylurea Initiators from the NDSS

	Metformin initiators	**Sulfonylurea initiators**	**Total**
	(n=102,737)	**(n=6,836)**	**(n=109,573)**
Age, years (mean±SD)	58.7±13.2	65.7±14.6	59.2±13.4
18-49	26,195 (25.5)	1,015 (14.8)	27,210 (24.8)
50-74	65,426 (63.7)	3,811 (55.7)	69,237 (63.2)
75-99	11,116 (10.8)	2,010 (29.4)	13,126 (12.0)
Sex, female n(%) [a]	45,634 (44.4)	3,021 (44.2)	48,655 (44.4)
Comorbidity score (median [IQR]) [b]	3 (2—5)	4 (2—7)	3 (2—5)
Number of comorbidities [b]			
0	6,225 (6.1)	399 (5.8)	6,624 (6.0)
1-2	30,042 (29.2)	1,515 (22.2)	31,557 (28.8)
3-4	30,389 (29.6)	1,567 (22.9)	31,956 (29.2)
5+	36,081 (35.1)	3,355 (49.1)	39,436 (36.0)
ARIA score			
1. Major urban	67,853 (66.0)	4,848 (70.9)	72,701 (66.3)
2. Inner regional	22,027 (21.4)	1,171 (17.1)	23,198 (21.2)
3. Outer regional	10,923 (10.6)	610 (8.9)	11,533 (10.5)
4. Remote	1,265 (1.2)	116 (1.7)	1,381 (1.3)

5. Very remote	669 (0.7)	91 (1.3)	760 (0.7)
SEIFA score (mean±SD)	2.94±1.40	2.98±1.44	2.94±1.40
1. Most disadvantaged	21,300 (20.7)	1,497 (21.9)	22,797 (20.8)
2.	20,589 (20.0)	1,251 (18.3)	21,840 (19.9)
3.	22,782 (22.2)	1,402 (20.5)	24,184 (22.1)
4.	19,057 (18.5)	1,274 (18.6)	20,331 (18.6)
5. Least disadvantaged	19,009 (18.5)	1,412 (20.7)	20,421 (18.6)
Congestive heart failure	5,250 (5.1)	946 (13.8)	6,196 (5.7)
Nicotine dependence	3,189 (3.1)	124 (1.8)	3,313 (3.0)
Depression	23,023 (22.4)	1,420 (20.8)	24,443 (22.3)
Systemic corticosteroids	6,226 (6.1)	884 (12.9)	7,110 (6.5)
Antipsychotics	3,581 (3.5)	231 (3.4)	3,812 (3.5)
Lipid-lowering medication	50,293 (49.0)	3,452 (50.5)	53,745 (49.0)
Hypertension	49,632 (48.3)	3,614 (52.9)	53,246 (48.6)
End stage renal disease	69 (0.1)	250 (3.7)	319 (0.3)
Time between T2D diagnosis and index date, (median±[IQR]), years	0.2 (0.0—4.7)	4.4 (0.1—9.9)	0.3 (0.0—5.0)
Time between T2D diagnosis and index date			
No delay	25,115 (24.4)	966 (14.1)	26,081 (23.8)
<1 year	32,205 (31.3)	1,117 (16.3)	33,322 (30.4)
1-2 years	5,607 (5.5)	351 (5.1)	5,958 (5.4)

>2 years	39,810 (38.7)	4,402 (64.4)	44,212 (40.3)
Aboriginal or Torres Strait Islander status			
Yes	2,995 (2.9)	212 (3.1)	3,207 (2.9)
No	86,829 (84.5)	5,870 (85.9)	92,699 (84.6)
Unspecified	12,913 (12.6)	754 (11.0)	13,667 (12.5)

NDSS National Diabetes Services Scheme; T2D Type 2 Diabetes; ARIA Accessibility/ Remoteness Index of Australia; SEIFA Socio-Economic Indexes for Areas; SD Standard deviation; IQR Interquartile Range

[a] Unless otherwise stated, figures are quoted as n(%)

[b] A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had T2D medications prescribed at baseline

Table 2. Factors Associated with Receiving Add-On Therapy or Treatment Switch Within One Year of Starting Metformin or Sulfonylurea

	Metformin Add-On		Metformin Switched		Sulfonylurea Add-On		Sulfonylurea Switched	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Age, years								
18-49								
50-74	0.77	(0.75—0.80)	0.84	(0.78—0.90)	0.70	(0.62—0.79)	0.69	(0.58—0.82)
75-99	0.57	(0.54—0.61)	1.05	(0.93—1.17)	0.44	(0.38—0.52)	0.42	(0.33—0.54)
Sex, female	0.84	(0.81—0.86)	1.42	(1.33—1.51)	0.98	(0.89—1.07)	1.00	(0.87—1.14)
Number of comorbidities [a]								
0								
1-2	0.87	(0.82—0.92)	1.06	(0.92—1.23)	0.91	(0.76—1.09)	0.95	(0.73—1.24)
3-4	0.80	(0.75—0.85)	1.11	(0.95—1.30)	0.71	(0.58—0.86)	0.84	(0.62—1.13)
5+	0.82	(0.76—0.88)	1.40	(1.18—1.66)	0.53	(0.42—0.66)	0.68	(0.49—0.96)

ARIA score								
1. Major Urban								
2. Inner Regional	0.99	(0.95—1.02)	1.08	(1.00—1.17)	0.95	(0.84—1.09)	1.17	(0.97—1.41)
3. Outer Regional	0.98	(0.93—1.03)	1.02	(0.91—1.13)	0.90	(0.76—1.07)	0.90	(0.70—1.17)
4/5 Remote and very remote	1.00	(0.90—1.11)	0.72	(0.56—0.95)	0.80	(0.59—1.09)	1.00	(0.65—1.52)
SEIFA index								
1. Most Disadvantaged								
2.	1.01	(0.96—1.05)	0.93	(0.85—1.03)	1.12	(0.97—1.29)	0.87	(0.70—1.09)
3.	0.99	(0.95—1.04)	0.90	(0.82—0.98)	1.04	(0.90—1.20)	1.02	(0.83—1.25)
4.	1.02	(0.97—1.07)	0.94	(0.85—1.04)	1.12	(0.97—1.29)	0.97	(0.78—1.20)
5. Least Disadvantaged	0.92	(0.87—0.96)	0.85	(0.77—0.95)	1.15	(1.00—1.33)	1.04	(0.84—1.28)
Congestive Heart Failure	1.29	(1.21—1.38)	1.27	(1.12—1.44)	1.23	(1.06—1.44)	0.91	(0.71—1.16)

Nicotine dependence	1.31	(1.22—1.42)	1.26	(1.07—1.48)	0.98	(0.69—1.38)	1.32	(0.86—2.02)
Depression	1.09	(1.05—1.13)	0.99	(0.91—1.07)	1.03	(0.91—1.17)	1.09	(0.91—1.31)
Systemic corticosteroids	1.15	(1.08—1.22)	1.47	(1.32—1.64)	1.10	(0.94—1.28)	1.26	(1.01—1.56)
Antipsychotics	1.21	(1.13—1.31)	0.91	(0.77—1.08)	1.60	(1.27—2.03)	1.17	(0.81—1.71)
Lipid-lowering medication	0.87	(0.84—0.90)	0.81	(0.75—0.87)	1.02	(0.91—1.13)	0.98	(0.83—1.14)
Hypertension	0.97	(0.93—1.00)	0.86	(0.80—0.92)	1.11	(1.00—1.24)	0.88	(0.75—1.04)
End stage renal disease	1.91	(1.23—2.97)	2.39	(1.19—4.79)	0.75	(0.55—1.02)	0.71	(0.45—1.13)
Time between T2D diagnosis and index date								
No time								
<1 year	0.86	(0.83—0.89)	0.87	(0.80—0.95)	0.80	(0.69—0.92)	0.90	(0.73—1.11)
1-2 years	0.77	(0.71—0.82)	0.84	(0.72—0.99)	0.54	(0.43—0.69)	0.60	(0.43—0.84)

>2 years	0.95	(0.92—0.99)	1.14	(1.05—1.23)	0.62	(0.55—0.69)	0.55	(0.46—0.65)
Aboriginal or Torres Strait Islander status	1.14	(1.06—1.24)	1.11	(0.93—1.33)	0.97	(0.72—1.29)	1.02	(0.68—1.54)

T2D Type 2 Diabetes; ARIA Accessibility/ Remoteness Index of Australia; SEIFA Socio-Economic Indexes for Areas; CI confidence interval; HR adjusted hazard ratio

[a] A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had T2D medications prescribed at baseline.

Table 3. Medications Added on or Switched to During the First Year after Metformin or Sulfonylurea Initiation

	Metformin Initiators		**Sulfonylurea Initiators**	
	Added on N=18,522	**Switched to N=4,081**	**Added on N=1,913**	**Switched to N=863**
Dipeptidyl peptidase-4 inhibitor (DPP-4I)	8,984 (48.5)	619 (15.2)	254 (13.3)	90 (10.4)
Sulfonylurea	6,104 (33.0)	2,514 (61.6)	NA	NA
Insulin	2,036 (11.0)	717 (17.6)	239 (12.5)	176 (20.4)
Metformin	NA	NA	1,199 (62.7)	505 (58.5)
Sodium-glucose co-transport inhibitor (SGLT-2I)	987 (5.3)	149 (3.7)	58 (3.0)	15 (1.7)
Glucagon-like peptide-1 agonist (GLP-1A)	349 (1.9)	46 (1.1)	13 (0.7)	5 (0.6)
Fixed-Dose-Combination product (FDC)	NA [a]	NA [a]	127 (6.6)	63 (7.3)
Thiazolidinedio	39 (0.2)	20 (0.5)	15 (0.8)	3 (0.3)

ne (TZD)				
Acarbose	23 (0.1)	16 (0.4)	8 (0.4)	6 (0.7)

[a] All FDC products available during the time of this study contained metformin plus another glucose-lowering medication. When individuals from the metformin cohort commenced an FDC, it was considered an addition/ switch with respect to the non-metformin component.

3.7 Figures

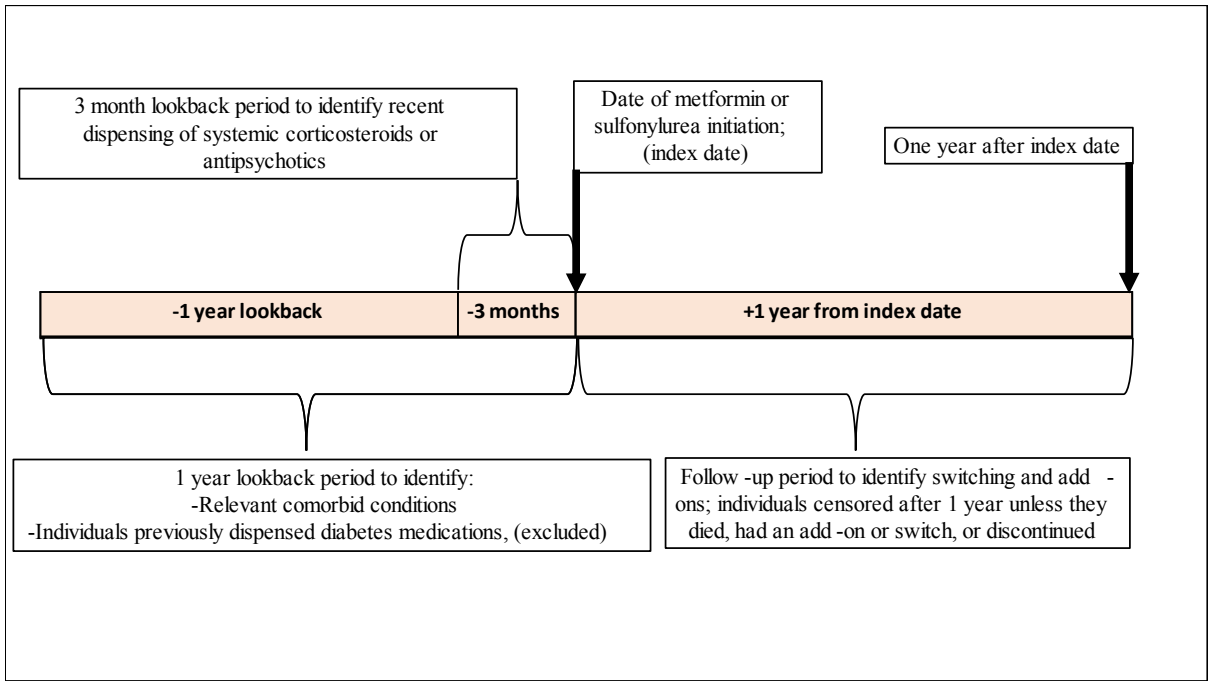

Figure 1. An illustration depicting the study design

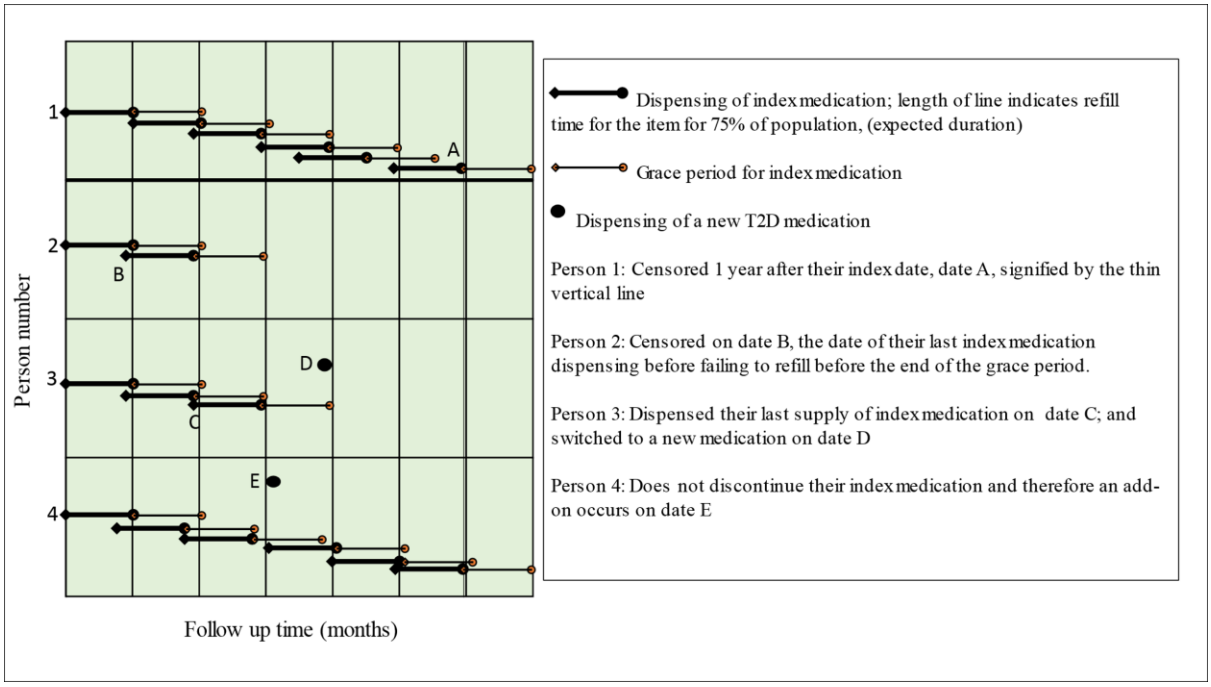

Figure 2. Illustration through examples how additions and switches were identified

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3.9 Supplementary material

Appendix A: RxRisk-V categories

Comorbidity or Condition	Anatomical Therapeutic Chemical Classification codes
Congestive heart failure	(C03CA01-C03CC01) AND (C09AA01-C09AA16 OR C09CA01-C09CX99), C03DA04, C07AB07, C07AG02, C07AB12, C09DX04, C07AB02 [a]
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX26
Diabetes	A10AA01-A10BX08
End stage renal disease	B03XA01-B03XA03, V03AE02, V03AE03, V03AE05
Hyperlipidaemia	C10AA01-C10BX12
Hypertension	C02AB01-C02AC05, C02DB01-C02DB04, C03AA01-C03BA11, C03BB04, C03CA01-C03CC01, C03DA01-C03DA03, C03DB01-C03DB02, C03EA01-C03EA14, C09AA01-C09AA16, C09BA02-C09BA15, C09CA01-C09CA10, C09DA01-C09DA09
Nicotine dependence	N07BA01-N07BA03, N06AX12

[a] Metoprolol, (ATC code C07AB02); PBS item codes were used to identify the indication. PBS codes 8732N, 8733P, 8734Q and 8735R indicated congestive heart failure.

Appendix B: Sensitivity Analysis in Concessional Population with 2 Year Lookback Period

Table B1. Characteristics of Concession Population of Metformin and Sulfonylurea Initiators from the NDSS

	Metformin initiators (n=45,026)	**Sulfonylurea initiators (n=2,657)**	**Total (n=47,683)**
Age, years (mean±SD)	63.4±13.4	69.8±13.3	63.8±13.5
18-49	7,784 (17.3)	234 (8.8)	8,018 (16.8)
50-74	29,071 (64.6)	1,402 (52.8)	30,473 (63.9)
75-99	8,171 (18.1)	1,021 (38.4)	9,192 (19.3)
Sex, female n(%) [a]	22,240 (49.4)	1,254 (47.2)	23,494 (49.3)
Comorbidity score (median [IQR]) [b]	5 (3—6)	6 (3—8)	5 (3—6)
Number of comorbidities [b]			
0	1,098 (2.4)	70 (2.6)	1,168 (2.4)
1-2	8,103 (18.0)	363 (13.7)	8,466 (17.8)
3-4	12,950 (28.8)	551 (20.7)	13,501 (28.3)
5+	22,875 (50.8)	1,673 (63.0)	24,548 (51.5)
ARIA score			
1. Major urban	27,617 (61.3)	1,789 (67.3)	29,406 (61.7)
2. Inner regional	11,353 (25.2)	503 (18.9)	11,856 (24.9)
3. Outer regional	5,341 (11.9)	275 (10.4)	5,616 (11.8)
4. Remote	482 (1.1)	50 (1.9)	532 (1.1)

5. Very remote	233 (0.5)	40 (1.5)	273 (0.6)
SEIFA score (mean±SD)	2.7±1.4	2.8±1.4	2.7±1.4
1. Most disadvantaged	11,518 (25.6)	683 (25.7)	12,201 (25.6)
2.	10,106 (22.4)	507 (19.1)	10,613 (22.3)
3.	9,964 (22.1)	568 (21.4)	10,532 (22.1)
4.	7,418 (16.5)	473 (17.8)	7,891 (16.5)
5. Least disadvantaged	6,020 (13.4)	426 (16.0)	6,446 (13.5)
Congestive heart failure	3,522 (7.8)	487 (18.3)	4,009 (8.4)
Nicotine dependence	1,734 (3.9)	56 (2.1)	1,790 (3.8)
Depression	13,185 (29.3)	649 (24.4)	13,834 (29.0)
Systemic corticosteroids	6,722 (14.9)	636 (23.9)	7,358 (15.4)
Antipsychotics	2,903 (6.4)	143 (5.4)	3,046 (6.4)
Lipid-lowering medications	26,137 (58.0)	1,521 (57.2)	27,658 (58.0)
Hypertension	25,017 (55.6)	1,556 (58.6)	26,573 (55.7)
End stage renal disease	36 (0.1)	127 (4.8)	163 (0.3)
Time between T2D diagnosis and index date (median [IQR]),	0.1 (0.0—4.5)	3.1 (0.0—9.1)	0.1 (0.0—4.8)

years			
Time between T2D diagnosis and index date			
No delay	11,863 (26.3)	471 (17.7)	12,334 (25.9)
<1 year	15,025 (33.4)	621 (23.4)	15,646 (32.8)
1-2 years	1,935 (4.3)	100 (3.8)	2,035 (4.3)
>2 years	16,203 (36.0)	1,465 (55.1)	17,668 (37.1)
Aboriginal or Torres Strait Islander status			
Yes	1,496 (3.3)	98 (3.7)	1,594 (3.3)
No	37,971 (84.3)	2,284 (86.0)	40,255 (84.4)
Unspecified	5,559 (12.3)	275 (10.4)	5,834 (12.2)

NDSS National Diabetes Services Scheme; T2D Type 2 Diabetes; ARIA Accessibility/ Remoteness Index of Australia; SEIFA Socio-Economic Indexes for Areas; SD Standard deviation; IQR Interquartile Range

[a] Unless otherwise stated, figures are quoted as n(%)

[b] A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had T2D medications prescribed at baseline

Table B2. Factors Associated with Receiving Add-On Therapy or Treatment Switch Within One Year of Starting Metformin or Sulfonylurea in Concession Population

	Metformin Add-On		Metformin Switched		Sulfonylurea Add-On		Sulfonylurea Switched	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Age, years								
18-49								
50-74	0.71	(0.66—0.75)	0.89	(0.79—1.00)	0.66	(0.52—0.84)	0.88	(0.60—1.27)
75-99	0.56	(0.51—0.62)	0.96	(0.82—1.11)	0.44	(0.34—0.58)	0.64	(0.42—0.98)
Sex, female	0.84	(0.80—0.89)	1.43	(1.31—1.56)	1.06	(0.91—1.23)	1.06	(0.84—1.33)
Number of comorbidities [a]								
0								
1-2	0.72	(0.62—0.82)	0.91	(0.69—1.21)	0.74	(0.50—1.08)	0.62	(0.35—1.10)
3-4	0.66	(0.57—0.76)	0.97	(0.73—1.29)	0.52	(0.35—0.78)	0.50	(0.28—0.90)
5+	0.67	(0.57—0.78)	1.18	(0.87—1.59)	0.44	(0.28—0.68)	0.45	(0.24—0.84)
ARIA score								
1. Major Urban								
2. Inner Regional	0.95	(0.90—1.02)	1.04	(0.94—1.15)	0.86	(0.69—1.07)	1.31	(0.99—1.75)
3. Outer Regional	0.92	(0.84—1.00)	1.06	(0.93—1.22)	1.00	(0.77—1.30)	1.09	(0.74—1.62)

4/5 Remote and very remote	1.18	(0.99—1.42)	0.60	(0.39—0.93)	0.65	(0.38—1.10)	0.87	(0.40—1.88)
SEIFA index								
1. Most Disadvantaged								
2.	0.99	(0.92—1.07)	0.93	(0.82—1.05)	0.99	(0.79—1.25)	0.89	(0.63—1.25)
3.	0.98	(0.91—1.05)	0.93	(0.82—1.05)	0.95	(0.76—1.20)	1.04	(0.75—1.44)
4.	1.01	(0.94—1.10)	1.02	(0.90—1.17)	1.00	(0.79—1.26)	1.13	(0.81—1.59)
5. Least Disadvantaged	0.95	(0.87—1.04)	0.96	(0.83—1.12)	1.13	(0.88—1.44)	0.84	(0.56—1.25)
Congestive Heart Failure	1.30	(1.18—1.43)	1.24	(1.07—1.44)	1.30	(1.04—1.62)	0.71	(0.50—1.03)
Nicotine dependence	1.20	(1.07—1.34)	1.07	(0.86—1.32)	0.93	(0.54—1.59)	1.33	(0.67—2.61)
Depression	1.11	(1.05—1.18)	1.01	(0.91—1.11)	1.07	(0.88—1.29)	1.10	(0.83—1.45)
Systemic corticosteroids	1.16	(1.08—1.25)	1.19	(1.06—1.33)	1.00	(0.82—1.23)	1.23	(0.92—1.64)
Antipsychotics	1.20	(1.09—1.32)	0.96	(0.80—1.14)	1.60	(1.16—2.20)	0.99	(0.57—1.71)
Lipid-lowering	0.84	(0.79—0.89)	0.81	(0.73—0.89)	0.86	(0.72—1.03)	0.94	(0.73—1.22)

medications								
Hypertension	1.00	(0.95—1.06)	0.86	(0.79—0.95)	1.05	(0.88—1.26)	0.93	(0.71—1.20)
End stage renal disease	1.98	(0.99—3.97)	3.72	(1.66—8.31)	0.71	(0.45—1.12)	0.84	(0.45—1.56)
Time between T2D diagnosis and index date								
No time								
<1 year	0.86	(0.80—0.91)	0.91	(0.82—1.02)	0.84	(0.68—1.03)	0.84	(0.61—1.16)
1-2 years	0.73	(0.63—0.84)	0.86	(0.68—1.09)	0.47	(0.29—0.76)	0.40	(0.18—0.87)
>2 years	0.89	(0.83—0.94)	1.15	(1.04—1.28)	0.57	(0.47—0.69)	0.61	(0.46—0.81)
Aboriginal or Torres Strait Islander Status	1.24	(1.10—1.40)	0.90	(0.70—1.16)	0.85	(0.55—1.33)	0.69	(0.33—1.42)

T2D Type 2 Diabetes; ARIA Accessibility/ Remoteness Index of Australia; SEIFA Socio-Economic Indexes for Areas; CI confidence interval; HR adjusted hazard ratio

[a] A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had T2D medications prescribed at baseline.

Chapter 4: Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012-2016

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Wood, S.J., et al., *Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012–2016.* The Journal of Frailty & Aging, 2021.

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Impact of Age, Frailty, and Dementia on Prescribing for Type 2 Diabetes at Hospital Discharge 2012-2016

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Abstract

BACKGROUND: The risks of intensive blood glucose lowering may outweigh the benefits in vulnerable older people.
OBJECTIVES: Our primary aim was to determine whether age, frailty, or dementia predict discharge treatment types for patients with type 2 diabetes (T2D) and related complications. Secondly, we aimed to determine the association between prior hypoglycemia and discharge treatment types.
DESIGN, SETTING AND PARTICIPANTS: We conducted a cohort study involving 3,067 patients aged 65-99 years with T2D and related complications, discharged from Melbourne's Eastern Health Hospital Network between 2012 and 2016.
MEASUREMENTS: Multinomial logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CI) for the association between age, frailty, dementia and hypoglycemia, and being prescribed insulin-only, non-insulin glucose-lowering drugs (GLDs) or combined insulin and non-insulin GLDs compared to no GLD. International Classification of Diseases-10 codes were used to identify dementia status and prior hypoglycemia; frailty was quantified using the Hospital Frailty Risk Score.
RESULTS: Insulin-only, non-insulin GLDs, combined insulin and noninsulin GLDs, and no GLDs were prescribed to 19%, 39%, 20%, and 23% of patients, respectively. Patients >80 years were less likely than patients aged 65-80 to be prescribed any of the GLD therapies, (eg. non-insulin GLDs [OR 0.67; 95%CI 0.55-0.82]), compared to no GLD. Similarly, high vs. low frailty scores were associated with not being prescribed any of the three GLD therapies, (eg. non-insulin GLDs [OR 0.63; 95%CI 0.45-0.87]). However, dementia was not associated with discharge prescribing of GLD therapies. Patients with a hypoglycemiarelated admission were more likely than those not hospitalized with hypoglycemia to receive insulin-only (OR 4.28; 95%CI 2.89-6.31).
Conclusions:
Clinicians consider age and frailty when tailoring diabetes treatment regimens for patients discharged from hospital with T2D and related complications. There is scope to optimize prescribing for patients with dementia and for those admitted with hypoglycemia.

Key words: Type 2 diabetes, frailty, dementia.

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Introduction

The benefits of intensive glycemic control for preventing microvascular outcomes in middle and older age people with Type 2 diabetes (T2D) have been demonstrated in the ACCORD, ADVANCE, and VADT trials (1-3). However, intensive treatment is associated with an increased risk of hypoglycemia and does not improve survival or the incidence of macrovascular outcomes in people with limited life expectancies (1-3). The risks of intensive treatment may outweigh the benefits in frail older people (4). The guidelines of the American Diabetes Association (ADA) recommend less stringent glycemic targets of <8% and <8.5% (64 mmol/mol and 69 mmol/mol) for older individuals with complex and very complex health status (5). Similarly, Australian guidelines advise less intensive and individualized treatment for these patient groups (6). Nevertheless, UK data suggest that those who are frail and have dementia are treated with similar glucose-lowering drugs (GLDs) and with the aim to achieve similar glycemic targets as robust older people without dementia (7).

Frailty is an important complication of diabetes (8, 9), and is characterized by vulnerability to stressors and a reduced ability to maintain homeostasis (10). Frailty increases the risk of adverse drug events, including falls, disability and death (11). There are reciprocal relationships between hypoglycemia, dementia, and frailty (12). There have been calls for frailty status to guide treatment selection (13), with frail people with diabetes at 71% higher adjusted risk of all-cause hospitalization and twice the risk of mortality than non-frail people (14). Furthermore, older people with diabetes who develop dementia have three times the risk of hypoglycemia compared to those who do not develop dementia (15). The ACCORD-MIND study reported that cognitive decline over 20 months was associated with a higher risk of hypoglycemia regardless of treatment intensity (15).

Hospitalization represents an opportunity for clinicians to adjust T2D treatment regimens, although it is unclear to what extent hospital clinicians consider age, frailty and dementia in prescribing decisions. There is also a paucity of information about GLDs prescribed for older people who are frail and/ or live with dementia, who may have different goals of care and treatment benefits and risks (5, 6). The primary aim of this study was to determine whether age, frailty, or dementia predict discharge treatment types for patients with T2D and related complications. Our secondary aim was to determine the association between prior hypoglycemia and discharge treatment types.

Methods

Data source, study design, and study population

The study was conducted at Eastern Health, a large metropolitan public hospital network in Melbourne, with three acute and four subacute hospitals (1,423 beds) (16). Eastern Health services a catchment area of 750,000 people and recorded 1,175,249 patient episodes between July 2015 and June 2016 (16). Eastern Health implemented an Electronic Medical Record (EMR) with electronic prescribing (e-prescribing) in 2011 (17). EMR discharge prescriptions record all medications intended for use by a patient after being discharged from the hospital (17). Demographic information and discharge diagnoses were extracted by the health service's Decision Support Unit, which relies upon the standard practice of Clinical Coders within the Health information Unit (17). Diagnoses were recorded using International Classification of Diseases-10 (ICD-10) codes with up to 40 diagnoses per patient. Discharge medications were identified from the EMR using Anatomical Therapeutic Chemical (ATC) classification codes (18).
We conducted a cohort study of 3,067 adults aged between 65 and 99 years with T2D who were discharged from one of the Eastern Health hospital locations in Melbourne, Australia, between 2012 and 2016 with a principal diagnosis of T2D with a diabetes related complication.

Measures and definitions

Our study population included all patients with a principal diagnosis of T2D, identified using ICD-10 code E11, and an ICD-10 code (E11-E14) for a diabetes-related complication recorded at hospital discharge (index hospitalization) (18). Medications for T2D were broadly classified as insulins (ATC code A10A) or non-insulin GLDs (A10B). ATC codes used to identify GLDs classes are provided in Appendix A. A modified version of the Diabetes Complications Severity Index (DCSI) [19], which converts ICD-10 codes into a 13-level metric to quantify effects of diabetes on seven body systems,

was used as an indicator of T2D severity. Although this version of the DCSI does not require laboratory data, validation studies have shown that its capacity to predict diabetes severity is comparable to other versions which do (19, 20). The DCSI is also likely to be indicative of diabetes duration as it has been shown that for every additional year of diabetes duration in people over 60 years, the adjusted odds of microvascular disease increases by 6% ($p<0.001$) (21).
We utilized a validated Hospital Frailty Risk Score, which categorizes people into three frailty categories based on the sum of weighted scores identified from International Classification of Diseases (ICD-10) codes (22). Gilbert et. al (2018) derived this score using 109 ICD-10 codes at least twice as prevalent in frail versus non-frail patients weighted according to how strongly they predict frailty (22). Codes used to derive the Hospital Frailty Risk Score (HFRS) reflect conditions linked to frailty (for example, volume depletion, cognitive impairment, and falls) or conditions overrepresented in frail populations such as lung disease, heart conditions and elective cataracts. Cut-point scores of <5, 5-15, and >15, as published by Gilbert et. al. indicated low, moderate, and high degrees of frailty, respectively. ICD-10 codes used to identify dementia and hypoglycemia are given in Appendix B.

Statistical analysis

Baseline characteristics were presented as means with standard deviations (SDs), medians with interquartile ranges (IQRs) or as frequencies and percentages. Predictors of treatment initiation were estimated using multinomial logistic regression. Variables were included in the final model if the unadjusted p-value associated with the odds ratio (OR) was <0.25. We included age (65-80 and >80), frailty (low, moderate or high) and dementia in our regression model and estimated adjusted odds ratios (ORs) with 95% confidence intervals (CI), adjusted for sex, index year, DCSI score, congestive cardiac failure (CCF), myocardial infarction (MI), renal disease, transient ischemic attack (TIA) or stroke, and hypoglycemia, (ICD-10 codes for comorbidities given in Appendix B). Variance Inflation Factors (VIF) with a cut-off of 2 were used to assess collinearity between the variables in the model. Statistical differences were evaluated using Pearson's chisquared test and ANOVA for categorical and continuous variables, respectively. We excluded the Charlson Comorbidity Index (CCI) from our adjusted model because it was collinear with several comorbidities in our model, though it is included in Table 1 for completeness. Comorbidities and concomitant medications were not included in the same model because concomitant medications were conceptualized as intermediate variables in the causal pathway between the comorbidity and the diabetes treatment regimen.
All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Eastern Health and Monash University Human Research Ethics Committees (study number LR41/2017).

Results

Cohort Characteristics

Of the 3,067 people hospitalized with T2D, 19% were prescribed insulin-only, 39% non-insulin GLDs, 20% insulin and non-insulin combinations and 23% no GLDs (Table 1). Slightly less than half of the cohort were female (48%), and the mean age of the cohort was 78.6 years (SD 7.8). Patients not prescribed GLDs were older (81.0, SD 8.1) than those prescribed non-insulin GLDs (78.3, SD 7.7), insulin only (78.2, SD 7.3), or combination therapy (76.5, SD 7.3). Based on ICD10 codes, 9% of the cohort had a dementia diagnosis, and 11% had been hospitalized with hypoglycemia.
Frailty scores were non-normally distributed, therefore medians and interquartile ranges (IQR) were reported. The median frailty score for the study population was 5.8 (IQR 2.510.2), with median frailty scores being higher amongst those who were not prescribed GLDs (6.9, IQR 3.0-11.5) and lower amongst those prescribed combinations (5.3, IQR 2.3-9.3), (Table 1). The Pearson correlation coefficient between age and frailty scores was 0.23 ($p<0.0001$).

Figure 1a) shows that 69.7% of patients prescribed insulin-only therapy had a DCSI score >1, $p<0.0001$. Figure 1b) indicates that 21.6% and 16.0% of the insulinonly and combination therapy groups had a documented prior hypoglycemia during their index hospitalization. In contrast, 5.7% and 6.7% of individuals receiving no GLD and noninsulin hypoglycemic agents had a documented episode of hypoglycemia, $p<0.0001$. Patients in the combination group were least likely (9.5%), to have a HFRS >15, $p<0.0001$ and to have dementia (4.3%), $p=0.0002$, (Figure 1c). Those with HFRS >15 were most likely (12.5%) to have had an episode of hypoglycemia, but this was not significantly higher than the other groups, $p=0.16$ (Figure 1d).

Table 1. Demographic and clinical characteristics of people over 65 years with Type 2 diabetes and a primary diagnosis of a diabetes related complication, by prescribed discharge medication

	Total (n=3,067)	No Type 2 Diabetes Medication (n=708)	Insulin Only Therapy (n=570)	Non-insulin Therapy (n=1,188)	Combination Therapy (n=601)	p-value*
Mean age, years ±SD	78.6±7.8	81.0±8.1	78.2±7.3	78.3±7.7	76.5±7.3	<0.0001
Age, years n (%)						<0.0001
65-80	1,787 (58.3)	324 (45.8)	337 (59.1)	696 (58.6)	430 (71.5)	
>80	1,280 (41.7)	384 (54.2)	233 (40.9)	492 (41.4)	171 (28.5)	
Median frailty score, (IQR)	5.8 (2.5-10.2)	6.9 (3.0-11.5)	6.1 (3.2-10.4)	5.3 (2.1-10.0)	5.3 (2.3-9.3)	<0.0001
Frailty category						
Low (<5)	1,336 (43.6)	257 (36.3)	237 (41.6)	556 (46.8)	286 (47.6)	
Medium (5-15)	1,379 (45.0)	343 (48.4)	263 (46.1)	515 (43.4)	258 (42.9)	
High (>15)	352 (11.5)	108 (15.3)	70 (12.3)	117 (9.8)	57 (9.5)	
Sex, female	1,467 (47.8)	375 (53.0)	283 (49.6)	556 (46.8)	253 (42.1)	0.0008
Index year						<0.0001
2012	847 (27.6)	148 (20.9)	202 (35.4)	325 (27.4)	172 (28.6)	
2013	518 (16.9)	102 (14.4)	106 (18.6)	201 (16.9)	109 (18.1)	
2014	564 (18.4)	129 (18.2)	94 (16.5)	232 (19.5)	109 (18.1)	
2015	490 (16.0)	125 (17.7)	90 (15.8)	166 (14.0)	109 (18.1)	
2016	648 (21.1)	204 (28.8)	78 (13.7)	264 (22.2)	102 (17.0)	
Median DCSI score, (IQR)	2 (1-3)	2 (0-3)	2 (1-4)	1 (0-3)	2 (1-3)	<0.0001
DCSI score						
0-1	1,425 (46.5)	351 (49.6)	173 (30.4)	628 (52.9)	273 (45.4)	
>1	1,642 (53.5)	357 (50.4)	397 (69.6)	560 (47.1)	328 (54.6)	
Median CCI, (IQR)	2 (1-4)	2 (1-4)	4 (2-5)	2 (1-4)	2 (1-4)	<0.0001
CCI						
≤2	1,600 (52.2)	362 (51.1)	215 (37.7)	692 (58.2)	331 (55.1)	
>2	1,467 (47.8)	346 (48.9)	355 (62.3)	496 (41.8)	270 (44.9)	
Chronic heart failure	479 (15.6)	94 (13.3)	132 (23.2)	168 (14.1)	85 (14.1)	<0.0001
Myocardial infarction	193 (6.3)	28 (4.0)	51 (8.9)	79 (6.6)	35 (5.8)	0.003
Renal disease	938 (30.6)	219 (30.9)	270 (47.4)	291 (24.5)	158 (26.3)	<0.0001
Dementia	269 (8.8)	93 (13.1)	47 (8.2)	90 (7.6)	39 (6.5)	<0.0001

Transient ischemic attack or stroke	246 (8.0)	52 (7.3)	37 (6.5)	110 (9.3)	47 (7.8)	0.19
Hospitalised with hypoglycaemia	338 (11.0)	40 (5.6)	123 (21.6)	79 (6.6)	96 (16.0)	<0.0001

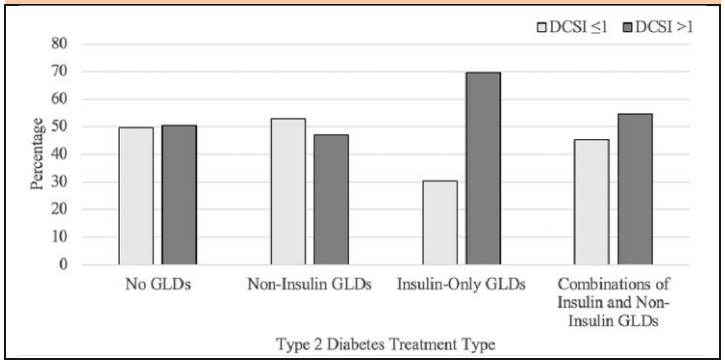
SD Standard deviation; IQR Inter Quartile Range; DCSI Diabetes Complications Severity Index; CCI Charlson Comorbidity Index. Data are presented as n(%). Non-insulin therapy included: metformin, sulfonylureas, acarbose, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP-4Is), glucagon-like peptide-1 agonists (GLP-1As), sodium-glucose cotransporter-2 inhibitors (SGLT-2Is), and fixed-dose combinations (FDC); *P-values were calculated using the Pearson's chi-squared test and ANOVA for categorical and continuous variables, respectively.

Predictors of Prescribed Anti-Hyperglycemic Therapy

People aged >80 versus those aged 65-80 were less likely to be prescribed insulin only (OR 0.54 95%CI 0.42-0.69), noninsulin GLDs only (OR 0.67 95%CI 0.55-0.82) or combinations of the two (OR 0.37 95%CI 0.29-0.47), compared to no GLDs (Table 2, Figure 2a). People with high frailty scores, compared to low scores, were less likely to be prescribed insulin only (OR 0.62 95%CI 0.42-0.91), non-insulin GLDs (OR 0.63 95%CI 0.45-0.87), or combinations of the two (OR 0.65 95%CI 0.43-0.96), compared to no GLDs (Table 2, Figure 2b).

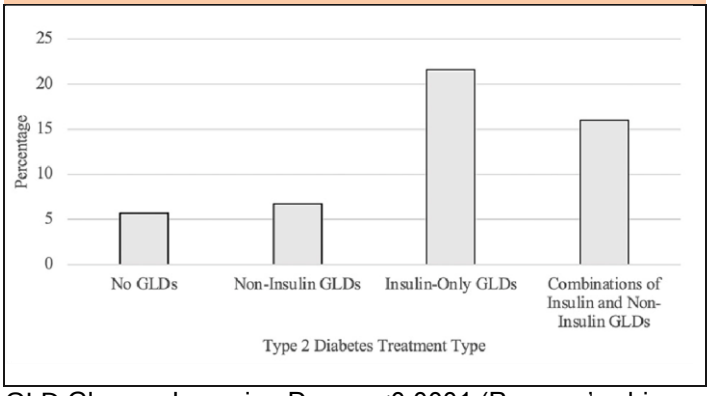
People with dementia were less likely to be prescribed non-insulin GLDs (OR 0.73 95%CI 0.53-1.01) or insulin and non-insulin GLD combinations (OR 0.72 95%CI 0.471.10) compared to no GLDs, although these results were nonstatistically significant (Table 2). People hospitalized with hypoglycemia, were more likely to receive insulin only (OR 4.28 95%CI 2.89-6.31) or combinations of insulin and noninsulin GLDs, (OR 3.15 95%CI 2.11-4.69), compared to no GLDs.

Figure 1a. Proportion of patients in each treatment group with baseline DCSI scores ≤1 or >1



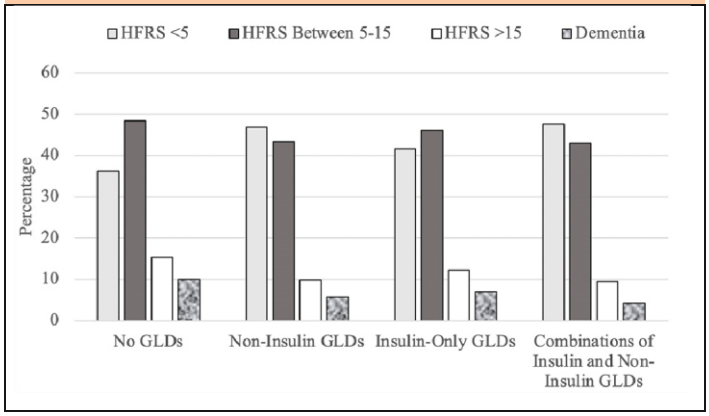
DCSI Diabetes Complications Severity Index; GLD Glucose Lowering Drug; p<0.0001 (Pearson's chi-squared test)

Figure 1b. Proportions of patients in each treatment group with a diagnosis of hypoglycemia recorded during index hospitalization



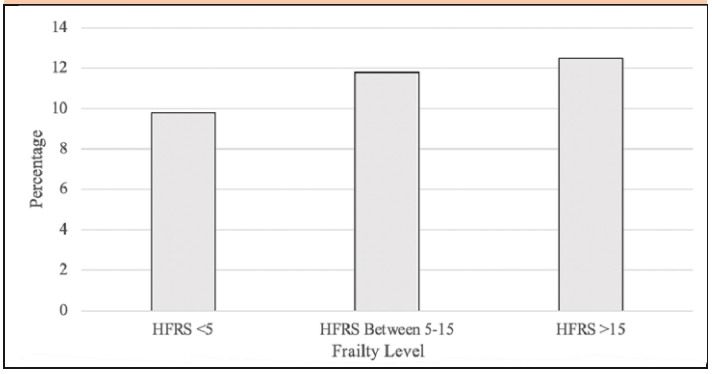
GLD Glucose Lowering Drug; p<0.0001 (Pearson's chi-squared test)

Figure 1c. Proportions of patients in each treatment group within each of the three frailty categories or with a diagnosis of dementia at baseline



HFRS Hospital Frailty Risk Score; GLD Glucose Lowering Drug; p<0.0001 for HFRS categories, p=0.0002 for dementia (Pearson's chi-squared test)

Figure 1d. Proportion of patients in frailty categories with hypoglycemia diagnosis at index discharge



HFRS Hospital Frailty Risk Score; p=0.16 (Pearson's chi-squared test)

Types of T2D Therapy Prescribed

The most commonly prescribed insulin types within the group receiving insulin-only therapy were mixed (64.7%), fast acting (30.0%) and long-acting (29.8%), with most individuals being prescribed either 1 (71.6%) or 2 (28.1%) different insulin products (Appendix C). Within the group receiving combination therapy, mixed (51.4%), long-acting (41.4%), and fast-acting (17.1%) insulins were most likely to be prescribed. All individuals in this group were prescribed either one (83.5%) or two (16.5%) types of insulin.

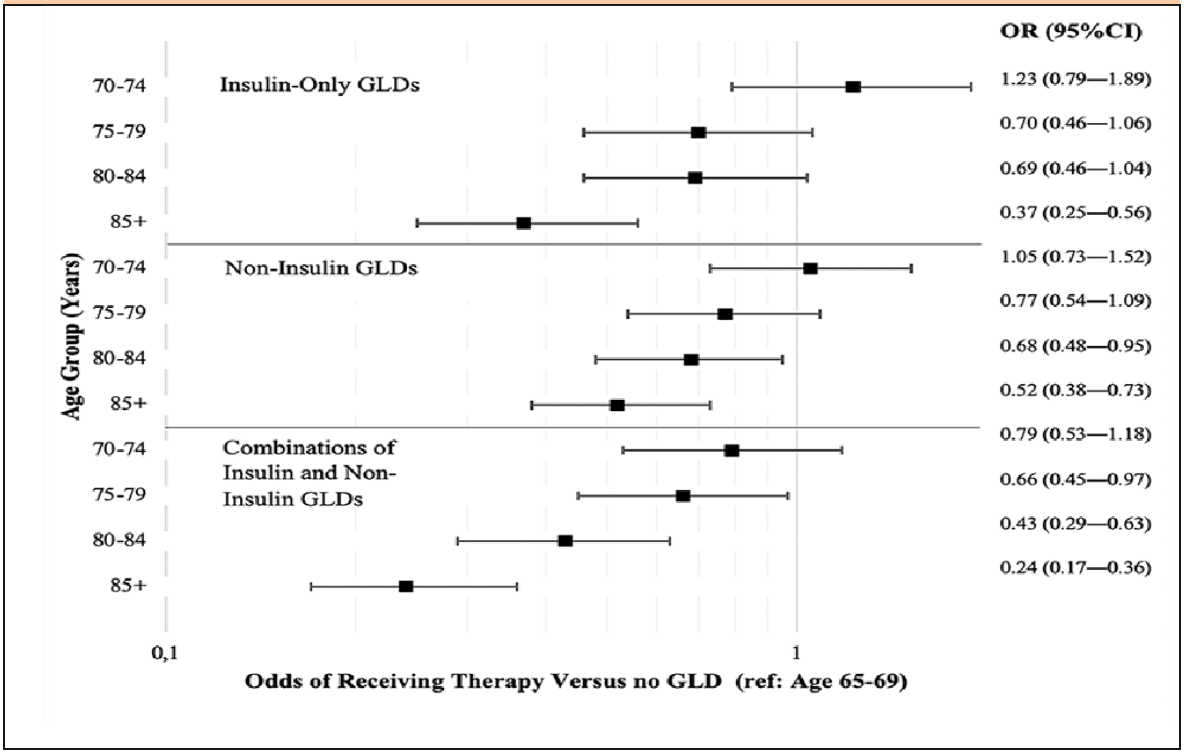
People in the non-insulin GLD group were most likely to be prescribed either metformin (69.9%) or a sulfonylurea (57.8%), with the majority being issued with either 1 (59.6%) or 2 (34.3%) non-insulin GLDs (Appendix C). Metformin (74.0%) and sulfonylureas (47.1%) were also the most commonly prescribed non-insulin GLDs in the combination group, and people in this group were most likely to receive either 1 (69.7%) or 2 (28.6%) non-insulin GLDs.

Table 2. Odds ratios for being prescribed Glucose Lowering Drugs (GLDs) versus No GLD at discharge amongst people with Type 2 diabetes and a primary diagnosis of a diabetes-related complication

	Insulin therapy		Non-insulin Therapy		Combination Therapy	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Age, years						
>80 vs. 65-80	0.54	[0.42-0.69]	0.67	[0.55-0.82]	0.37	[0.29-0.47]
Frailty Score						
Moderate vs. Low	0.77	[0.59-0.99]	0.79	[0.64-0.98]	0.79	[0.61-1.01]
High vs. Low	0.62	[0.42-0.91]	0.63	[0.45-0.87]	0.65	[0.43-0.96]
Dementia	0.98	[0.65-1.47]	0.73	[0.53-1.01]	0.72	[0.47-1.10]
Hospitalised with hypoglycaemia	4.28	[2.89-6.31]	1.24	[0.83-1.85]	3.15	[2.11-4.69]
Sex						
Female vs. male	0.96	[0.76-1.22]	0.80	[0.66-0.97]	0.70	[0.56-0.88]
Index year						
2013 vs. 2012	0.76	[0.53-1.08]	0.95	[0.70-1.30]	1.00	[0.70-1.43]
2014 vs. 2012	0.55	[0.39-0.78]	0.86	[0.64-1.15]	0.78	[0.56-1.11]
2015 vs. 2012	0.56	[0.39-0.79]	0.62	[0.46-0.85]	0.80	[0.57-1.14]
2016 vs. 2012	0.35	[0.24-0.49]	0.57	[0.43-0.75]	0.44	[0.32-0.62]
DCSI score						
>1 vs. 0-1	1.44	[1.08-1.92]	0.80	[0.63-1.01]	1.11	[0.84-1.45]
Chronic heart failure	1.34	[0.96-1.86]	1.21	[0.89-1.64]	1.04	[0.73-1.49]
Myocardial infarction	1.90	[1.15-3.14]	1.92	[1.21-3.03]	1.53	[0.90-2.61]
Renal disease	1.83	[1.40-2.39]	0.80	[0.63-1.01]	0.82	[0.62-1.08]
Transient ischemic attack or stroke	0.95	[0.59-1.51]	1.55	[1.07-2.25]	1.08	[0.69-1.68]

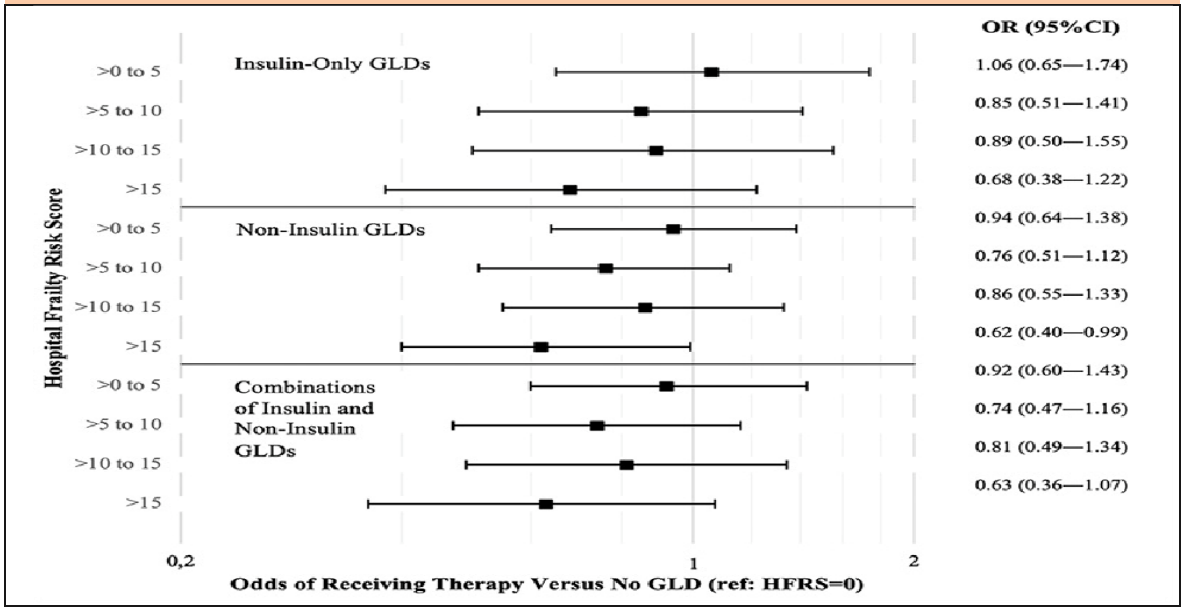
DCSI: Diabetes Complications Severity Index; bold indicates a statistically significant result.

Figure 2a. Forest plot of type of antihyperglycemic therapy prescribed for people over 65 years, hospitalised with Type 2 diabetes and a related complication, by age group



OR Odds Ratio; CI Confidence Interval; GLD Glucose Lowering Drug.

Figure 2b. Forest plot of type of antihyperglycemic therapy prescribed for people over 65 years, hospitalised with Type 2 diabetes and a related complication, by frailty score



OR Odds Ratio; CI Confidence Interval; GLD Glucose Lowering Drug; HFRS Hospital Frailty Risk Score.

Discussion

This was the first study to investigate how age, frailty, and dementia predict hospital discharge prescribing for people with T2D. Older age and frailty predicted less intense treatment of T2D, people 80 and older were 63% less likely than those aged between 65-80 years to receive combinations of insulin and non-insulin GLDs, compared to no GLDs. Moreover, frail people were 35% less likely than robust people to be discharged on a combination of insulin and non-insulin GLDs versus no GLDs.

Our findings suggest clinicians consider age and frailty by tailoring diabetes treatment regimens. This is encouraging because frail older individuals are more vulnerable to adverse events, such as hypoglycemia and mortality (23). In addition, weight loss and sarcopenia associated with frailty (12) may be exacerbated by changes in the natural history of T2D, which shifts from a progressive to a regressive course in individuals who are frail (24). Older age is a well-known risk factor for hypoglycemia, and our findings demonstrate adherence to national and international prescribing guidelines, which advise that individuals with shorter life expectancy derive limited benefits from stringent glycemic targets (5, 6). Older people with T2D are also less likely to recognize early signs of hypoglycemia due to reduced awareness of hypoglycemic symptoms and slower reaction times than younger counterparts (25). Severe hypoglycemia can cause sudden cardiovascular death, and episodes of mild hypoglycemia can cause falls, fractures, cognitive impairment, seizures, coma, cardiovascular events, and arrhythmias (23). National estimates in the US indicate that insulin users >80 years are hospitalized for hypoglycemia or insulin-related errors at five times the rate of insulin users aged 45-64 years (26). Reasons postulated for this increase include reduced food intake and administration of the wrong insulin product (26).

People with dementia tended to be less likely to be discharged on insulin and non-insulin GLD combinations compared to no GLDs. Although not statistically significant, this result suggests possible increasing awareness of the need to align treatment with goals of care (27). It may also reflect prescribers' awareness that individuals with dementia have a reduced capacity to manage complex regimens, particularly those involving insulin, due to difficulties in remembering dosage directions, to take doses on time or to take with food. Insulin and oral hypoglycemic agents such as sulfonylureas are considered high-risk medications and are associated with preventable hospitalizations, including among residents of nursing homes and long-term care facilities.

People hospitalized with hypoglycemia were over three times as likely to be prescribed insulin and non-insulin GLD combinations and over four times as likely to be prescribed insulin only compared to no GLDs. While we were not able to assess the clinical appropriateness of T2D regimens for individual patients, this suggests a possible opportunity for treatment de-intensification in 'at risk' population groups. It is also possible that there is scope for regimen simplification, as 28.5% of individuals prescribed insulin only and 16.5% prescribed combination treatment used at least two insulin products. It has been shown that simplification of multiple insulin regimens to basal insulin glargine only, reduced duration of hypoglycemia by 65% after eight months (28).

Strengths and limitations

Our study analyzed five years of discharge prescribing data from a large public hospital network in Melbourne. To our knowledge, this is the first study to investigate the impact of age, frailty, and dementia status as predictors of T2D discharge treatment intensity. One limitation of this study is that the Hospital Frailty Risk Score was validated for individuals >75 years, whereas we included individuals ≥65 years. The Hospital Frailty Risk Score was calculated using ICD-10 codes including dementia and, therefore, it is possible that there was overlap between dementia and frailty. Prescribing patterns may have evolved since 2016, particularly with the introduction of sodium-glucose cotransporter-2 inhibitors (SGLT-2Is). We considered age, dementia, and frailty status as categorical rather than continuous variables. However, age, frailty and dementia severity are continuous and there is no evidence for specific cut-points to define prescribing appropriateness in relation to these parameters. Lack of data on diabetes duration is a limitation. However, we presented the diabetes treatment according to less and more severe diabetes complications, which are related to diabetes duration (21). We did not have data on pre-admission treatment. However, we have presented the proportion of patients with documented prior hypoglycemia in each of the treatment groups. We hypothesized that prior hypoglycemia would prompt clinicians to modify treatment. Analyzing discharge prescribing is consistent with the treatment decision design in which cohorts are anchored at the point when treatment decisions are made (29). This is because medication regimens are typically evaluated during a hospital episode (29). Additionally, given that the sample comprised Australians who had been hospitalized, the results are not necessarily generalizable to all older patients with T2D across all clinical settings. We were not able to analyze data on HbA1C levels and ethnicity. Finally, a common limitation with the use of prescribing data, is that we do not know whether prescribed medications are actually taken by patients as directed.

Conclusion

Frail older people hospitalized with T2D and diabetes-related complications are less likely to be prescribed insulin-only GLDs, non-insulin GLDs or a combination of both, compared to no GLDs. Increasing age is also associated with receiving less intensive GLD regimens. Conversely, people hospitalized with hypoglycemia are considerably more likely to be discharged with a medication regimen which includes insulin. Clinicians appear to consider age and frailty when prescribing for people with T2D, but there is further opportunity for treatment de-intensification in 'at risk' groups.

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Conflicts of Interest: J.S.B. has received grant income paid to his employer from NHMRC, Australian Government Department of Health, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation, Yulgilbar Foundation, GSK Independent Medical Education and several aged care provider organizations. M.C reports personal fees from Nestlé, outside the submitted work. J.I. reports grants from AstraZeneca, Amgen, Dementia Australia Research Foundation, National Health and Medical Research Council, and National Breast Cancer Foundation, outside the submitted work. S.W., D.J.M., L.F., and C.K. have no competing interests to declare.

Ethical standards: This study was approved by the Eastern Health and Monash University Human Research Ethics Committees (study number LR41/2017).

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Appendix A: Anatomical Therapeutic Chemical (ATC) Codes Used to Identify Classes of Glucose Lowering Drugs

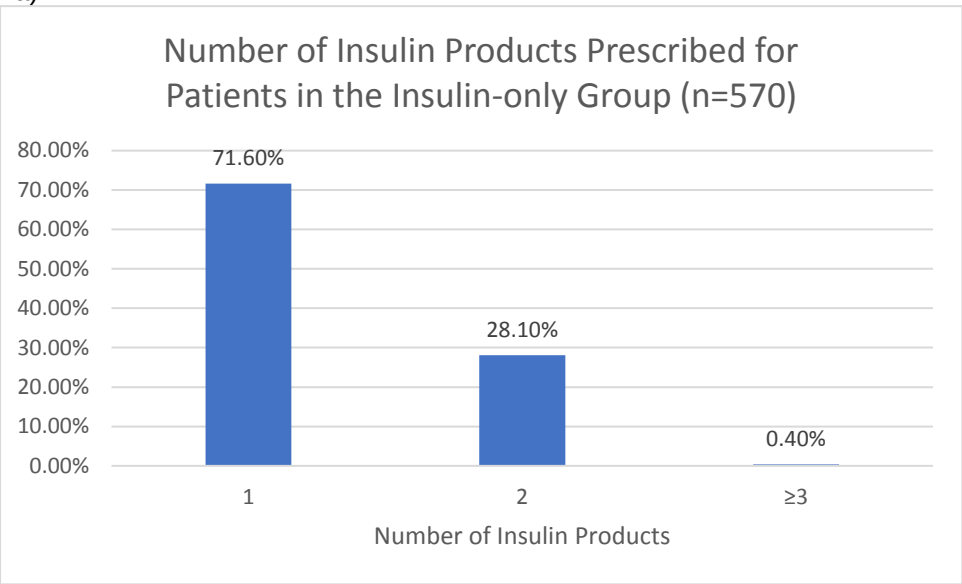
Class of Glucose-Lowering Drug	Anatomical Therapeutic Chemical codes used
Rapid-acting Insulin	A10AB
Intermediate-acting Insulin	A10AC
Mixed Insulin	A10AD
Slow-acting Insulin	A10AE
Metformin	A10BA
Sulfonylureas	A10BB
Fixed-Dose Combinations (FDC)	A10BD
Acarbose	A10BF
Thiazolidinediones	A10BG
Dipeptidyl Peptidase-4 Inhibitors (DPP-4Is)	A10BH
Glucagon-Like Peptide-1 Agonists (GLP-1As)	A10BJ
Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2Is)	A10BK, A10BX

Appendix B: International Classification of Diseases 10 Codes Used to Identify Comorbidities

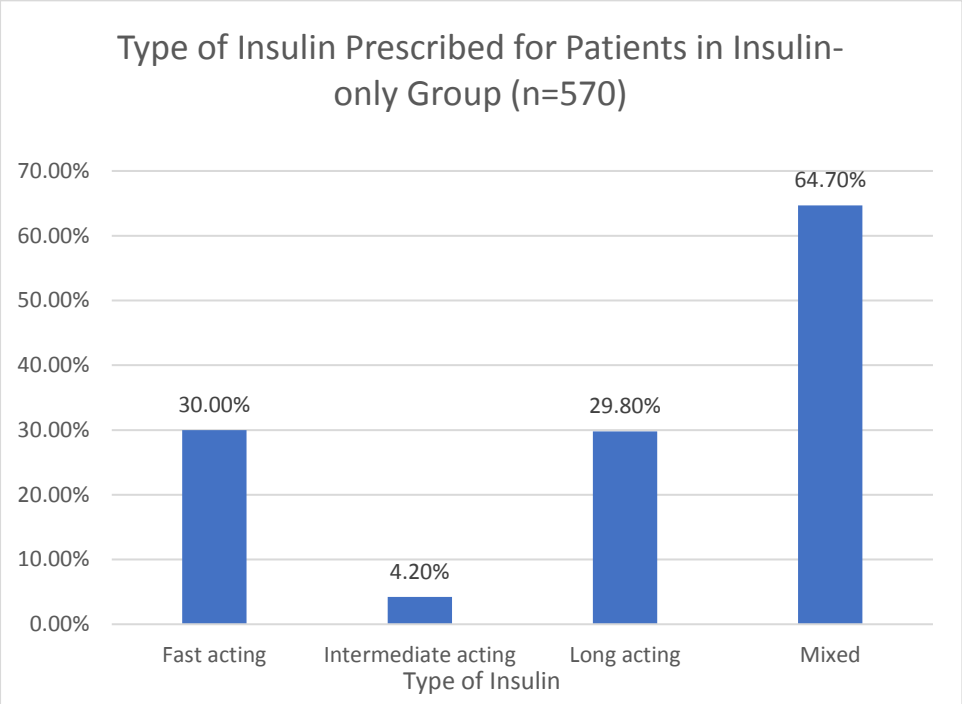
Comorbidity	International Classification of Diseases 10 codes used
Dementia	F00-F03, F05.1, G30, G31.1, U79.1
Hypoglycemia	E10.64, E11.64, E13.64, E14.64, E16.0-E16.2, T38.5
Chronic heart failure	I50
Myocardial infarction	I21-I22, I25.2
Renal disease	N01, N03, N052-N056, N072-N074, N18, N19, N25
Transient ischemic attack or stroke	G45.0-G45.2, G45.4, G45.8, G45.9, G46, I60-I66, I67.0-I67.2, I67.4-I67.9, I68.1, I68.2, I68.8, I69

Appendix C: Numbers and Types of Glucose-Lowering Drugs Prescribed

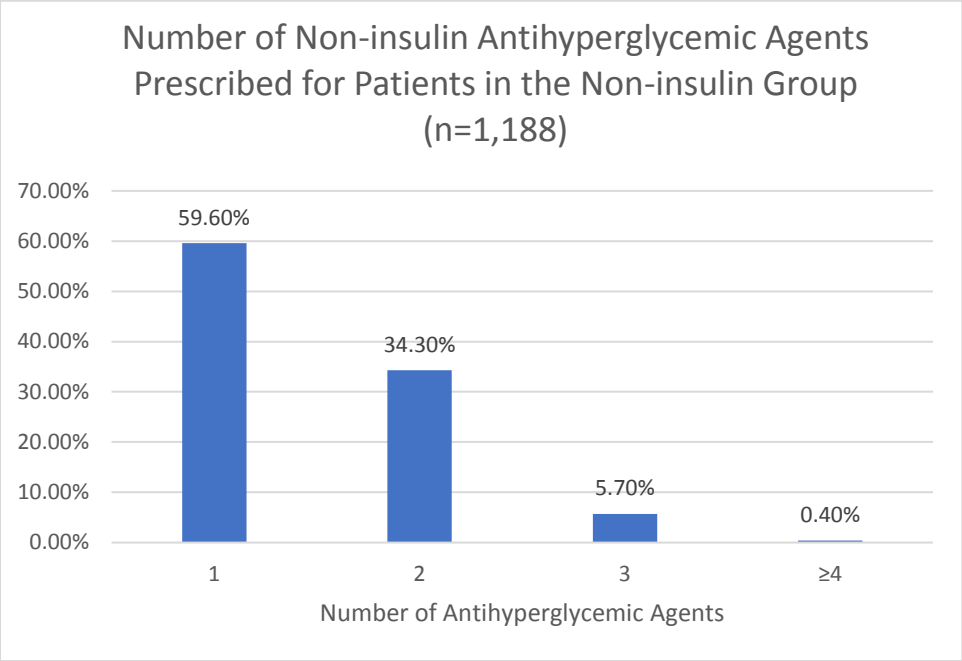
1a)



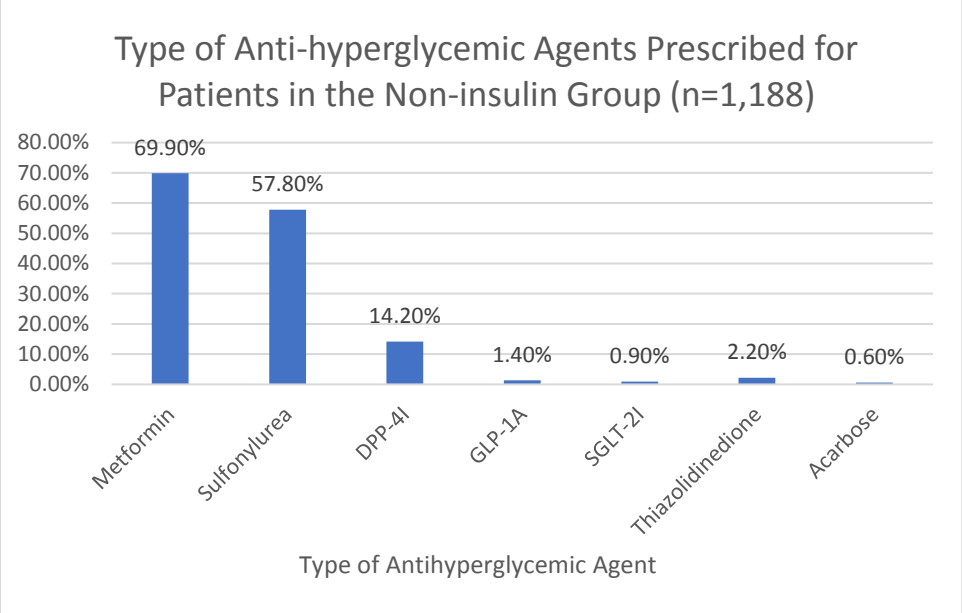
1b)



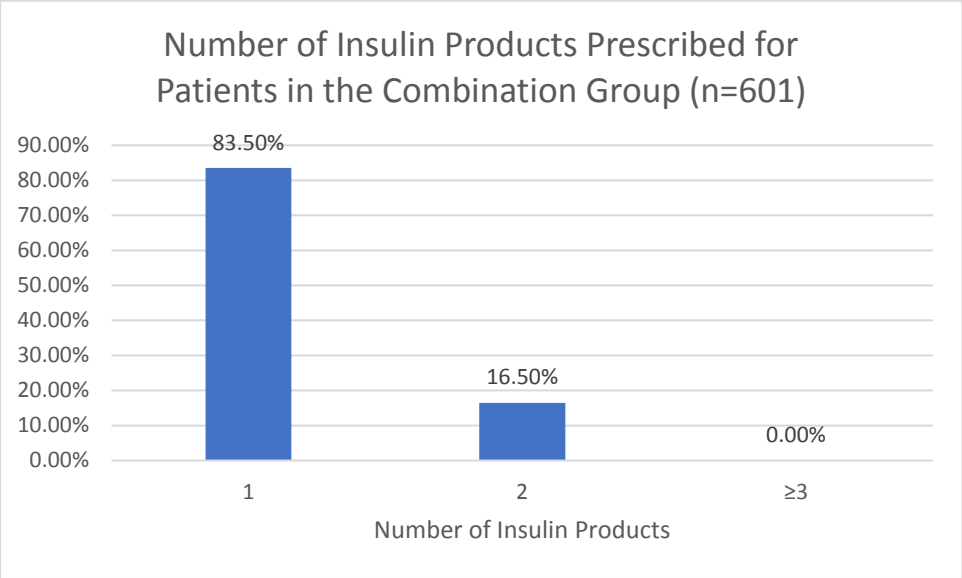
1c)


Number of Non-insulin Antihyperglycemic Agents Prescribed for Patients in the Non-insulin Group (n=1,188)
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
59.60%
34.30%
5.70%
0.40%
1
2
3
≥4
Number of Antihyperglycemic Agents

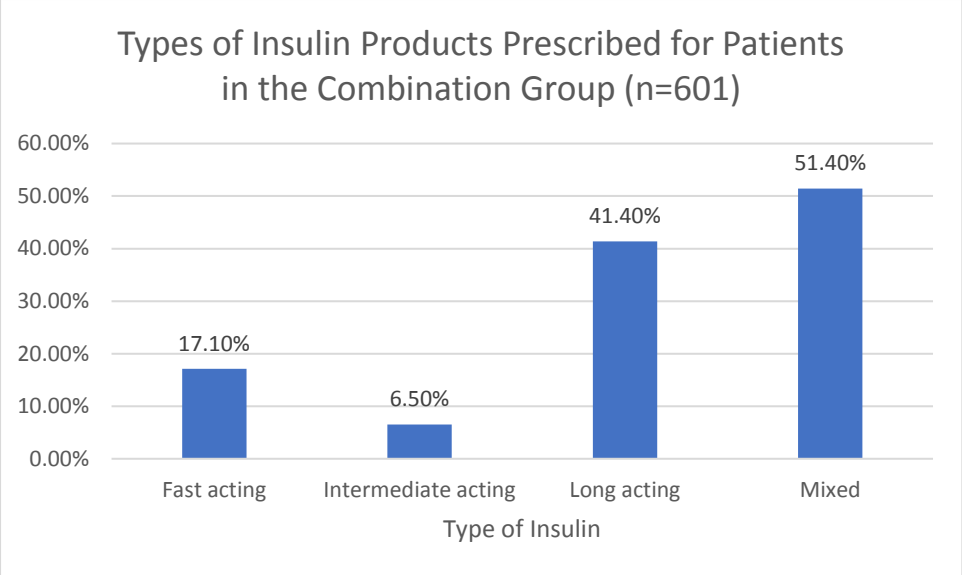
1d)


Type of Anti-hyperglycemic Agents Prescribed for Patients in the Non-insulin Group (n=1,188)
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
69.90%
57.80%
14.20%
1.40%
0.90%
2.20%
0.60%
Metformin
Sulfonylurea
DPP-4I
GLP-1A
SGLT-2I
Thiazolidinedione
Acarbose
Type of Antihyperglycemic Agent

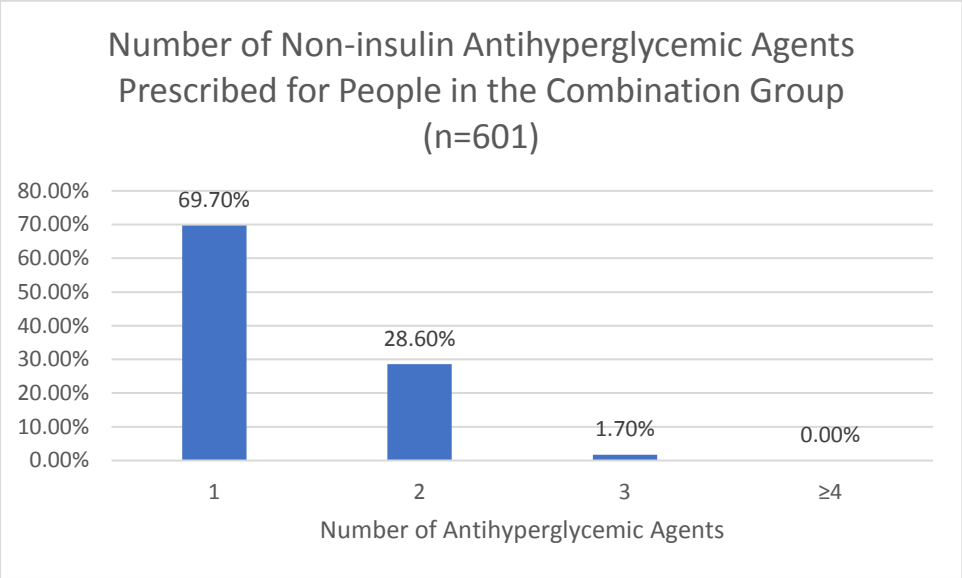
1e)


Number of Insulin Products Prescribed for Patients in the Combination Group (n=601)
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
83.50%
16.50%
0.00%
1
2
≥3
Number of Insulin Products

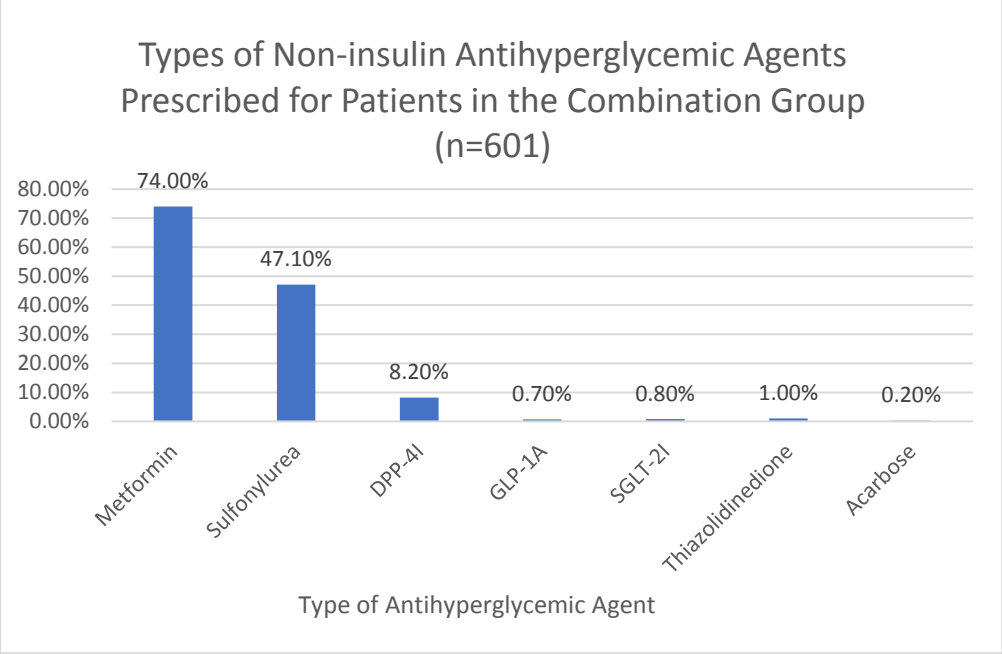
1f)


Types of Insulin Products Prescribed for Patients in the Combination Group (n=601)
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
17.10%
6.50%
41.40%
51.40%
Fast acting
Intermediate acting
Long acting
Mixed
Type of Insulin

1g)



1h)



GLD Glucose Lowering Drug; DPP-4I Dipeptidyl-Peptidase-IV Inhibitor; GLP-1A Glucagon Like Peptide-1 Agonist; SGLT-2I Sodium Glucose Cotransporter-2 Inhibitor

Chapter 5: Effectiveness of Sodium-Glucose Cotransporter-2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitors in Frail People with Diabetes

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5.1 Abstract

Objective: Sodium-glucose cotransporter-2 inhibitors (SGLT-2Is) reduce heart failure (HF) hospitalizations and major adverse cardiovascular events (MACE) in general type 2 diabetes populations. The objective of this study was to determine whether SGLT-2Is vs. dipeptidyl peptidase-4 inhibitors (DPP-4Is) are associated with reductions in MACE, HF hospitalizations and mortality in frail people with type 2 diabetes.

Research Design and Methods: We conducted a cohort study of all patients aged ≥30 years with type 2 diabetes discharged from a hospital in Victoria, Australia between July 2013 and June 2017 who received SGLT-2Is or DPP-4Is within 60 days of discharge. The 365-day follow-up commenced 60 days after initial discharge, and MACE, HF hospitalization and mortality were recorded. Cox proportional hazards regression with competing risks and stabilized inverse probability weights was used to generate hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were stratified into frailty quartiles according to Hospital Frailty Risk Scores.

Results: Of the 26,913 patients, (42% female and 5.2% ≥80 years) in the cohort, 3,132 (11.6%) received SGLT-2Is and 23,781 (88.4%) received DPP-4Is. MACE was less likely among SGLT-2I versus DPP-4I recipients in the combined first and second (HR 0.60; 0.46—0.78), third (HR 0.55; 95%CI 0.34—0.87) and fourth (HR 0.45; 95%CI 0.29—0.70) frailty quartiles. HF hospitalization (HR 0.72; 95%CI 0.41—1.29) and mortality (HR 0.97; 95%CI 0.62—1.53) risks for those in the third frailty quartile, did not differ between SGLT-2I and DPP-4I recipients.

Conclusion: SGLT-2Is may be preferred to DPP-4Is for preventing MACE in frail people with type 2 diabetes. In this population, there was no apparent difference

between SGLT-2Is and DPP-4Is for preventing HF hospitalizations and mortality. This finding provides evidence that SGLT-2Is may be a suitable alternative to DPP-4Is for frail people with type 2 diabetes.

Keywords: SGLT-2I, Frailty, Type 2 Diabetes, MACE

5.2 Introduction

Randomized controlled trials (RCTs) demonstrate sodium-glucose cotransporter-2 inhibitors (SGLT-2Is) reduce hospitalizations for heart failure (HF) and mortality in general older populations with type 2 diabetes [1-3]. However, despite an estimated 32% to 48% prevalence of frailty in people with diabetes [4], people who are frail are often excluded from RCTs. There is increasing interest in whether treatment benefits and risks in general older populations can be extrapolated to people who are frail [5]. This is important because frailty is a medical condition closely related to diabetes and a risk factor for diabetes-related complications [6].

Clinical practice guidelines recommend prescribing second-line therapies when metformin or sulfonylureas are not tolerated or are unsuccessful in controlling hyperglycemia [7-9], but clinicians treating frail older people with type 2 diabetes face challenges selecting appropriate second-line therapy. Systematic reviews have shown people who are frail have over 5-times higher odds of hospitalization and a 35% increased risk of mortality compared to non-frail individuals with diabetes [10]. SGLT-2Is and dipeptidyl peptidase-4 inhibitors (DPP-4Is) do not cause hypoglycemia, are administered orally [7], and may be preferred over sulfonylureas and insulin in people at high risk of hypoglycemia such as those who are frail [11]. We have previously demonstrated that people who are frail are less likely to be prescribed insulin at hospital discharge than those who are non-frail [12]. It remains unclear whether SGLT-2Is or DPP-4Is have the same benefits and risks in frail people with type 2 diabetes compared to non-frail people with type 2 diabetes.

In general populations of people with type 2 diabetes, meta-analyses have shown that DPP-4Is do not reduce the risk of major adverse cardiovascular events (MACE)

compared to placebo [13]. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction 53 (TIMI-53) trial concluded that the DPP-4I saxagliptin did not reduce ischemic events but increased HF hospitalizations by 27% [14]. Overall, however, there is no evidence that DPP-4Is increase the risk of MACE or HF [15]. In contrast, some cardiovascular benefits of SGLT-2Is are well established [1,2,16]. The Empagliflozin, Cardiovascular Outcomes, and Mortality in type 2 Diabetes (EMPA-REG OUTCOMES) trial [2] demonstrated 38% relative risk reduction in cardiovascular death, 32% reduction in all-cause mortality, and 35% reduction in HF hospitalizations. However, it was not shown to significantly affect rates of myocardial infarction (MI) or stroke [2]. A network meta-analysis by Fei et al. found that SGLT-2Is were associated with 17% lower odds of both cardiovascular and all-cause death compared to DPP-4Is [17].

To our knowledge, no studies to date have investigated whether frailty modifies the effect of SGLT-2Is on MACE, HF hospitalization, and mortality in people with type 2 diabetes. However, considering the advantages of SGLT-2Is reducing HF hospitalizations in people with type 2 diabetes, we hypothesized that benefits would be evident in this vulnerable population. The objective of this study was to determine whether SGLT-2Is, compared to DPP-4Is, prevent MACE, HF hospitalizations and mortality in frail people with type 2 diabetes.

5.3 Research design and methods

5.3.1 Data source, study design, and study population

We utilized data from the Victorian Admitted Episodes Dataset (VAED). This dataset contains demographic, administrative, and clinical information for all episodes of care across Victorian public and private hospitals, rehabilitation centres, extended care facilities, and day procedure centres [18]. Victoria is Australia's second most populous state with a population of 6.7 million. VAED data were liked to data on medication dispensing through Australia's Pharmaceutical Benefits Scheme (PBS). The PBS subsidizes the cost of medications dispensed through community pharmacies and at hospital discharge for all Australian citizens, residents, and visitors from countries with reciprocal health coverage. Data were also linked to the National Death Index for dates and causes of death. Data linkage was performed by the Australian Institute of Health and Welfare (AIHW). Ethics approval was acquired from AIHW Ethics Committee (EO2018-4-468) and Monash University Human Research Ethics Committee (14339).

We conducted a cohort study on the effects of SGLT-2Is compared to DPP-4Is in the prevention of MACE, HF hospitalization, and mortality during the first year after hospital discharge. The cohort comprised people aged ≥30 years with type 2 diabetes who were discharged from hospital between July 2013 and June 2017. We only included people who used metformin or sulfonylurea as their first-line treatment because Australian PBS regulations stipulate that SGLT-2Is or DPP-4Is can only be subsidized for people who have trialled one of these first line therapies without meeting glycemic targets. Additionally, this approach reduced the risk of confounding by disease severity. The use of metformin and sulfonylureas was captured from PBS dispensing at or 365 days prior to the initial discharge date (index date) (Figure 1).

Exposure to SGLT-2Is and DPP-4Is was assessed during a landmark period of 60 days after the index date for each patient (Figure 1). The landmark period methodology was chosen as it is the method of choice to minimize immortal-time bias [19]. Others have utilized 30 and 60 day landmark periods [19], however, we selected the more conservative 60-day period to capture the majority of SGLT-2I or DPP-4I users. This is because in Australia SGLT-2Is and DPP-4Is are usually dispensed in quantities that correspond to 28-30 days of treatment but some people miss doses or have additional supplies from a previous dispensing. The 365-day follow-up commenced after the 60-day landmark period. Patients who died or received both an SGLT-2I and a DPP-4I during the landmark period were excluded from the study. MACE outcomes during the landmark period were not recorded as outcomes, because there may have been insufficient time for the medications to exert an effect by this point (Figure 2).

5.3.2 Measures and definitions

Anatomical Therapeutic Chemical (ATC) codes were used to identify SGLT-2I (canagliflozin, empagliflozin, dapagliflozin and ertugliflozin) and DPP-4I (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) dispensings during the landmark period and to identify other relevant medications dispensed during the year before the index date (Appendix A). The latter included a range of cardiovascular medication classes as well as antipsychotics, owing to their effects on glucose levels. The International Classification of Diseases-10 (ICD-10) codes were used to identify diagnoses for type 2 diabetes (E11) as well as chronic diseases including cardiovascular conditions, dementia, and diabetic complications (Appendix B) [20]. These were identified using all available hospital admissions data, from 2006 until

the index date of each patient. Acute conditions such as severe hypoglycemia and conditions which can change substantially over time, such as cancer, were identified from the hospital admissions data using a one-year lookback period (Appendix B).

MACE has various definitions [21, 22], but we used the definition which captured the broadest possible range of cardiac outcomes. MACE was identified using ICD-10 codes (MI, HF hospitalization, and stroke) and ICD-10 procedure codes (Percutaneous Coronary Interventions [PCIs] with stents and Coronary Artery Bypass Grafts [CABGs] and revascularization; Appendix C). If a patient died during follow-up without hospitalization for MACE, and the ICD-10 code identifying their primary cause of death was indicative of MACE, then an event was recorded. If the primary cause of death was unrelated to MACE, then the person was deemed to have experienced a competing risk on the death date. In the HF hospitalization analysis, the ICD-10 code “I50” was considered an event, whereas all-cause death was recorded as a competing risk for those without hospital admission for HF. In the all-cause mortality analyses, the outcome was death due to any cause during the follow-up period. In all analyses, patients who did not experience an event or did not die were censored at 365 days after the end of the landmark period.

We utilized the validated Hospital Frailty Risk Score (HFRS). The HFRS quantifies frailty based on the sum of weighted scores identified from International Classification of Diseases (ICD-10) codes (Appendix D) [23]. Gilbert et. al (2018) derived this score using 109 ICD-10 codes at least twice as prevalent in frail versus non-frail patients weighted according to how strongly they predict frailty [23]. Codes used to derive the HFRS reflect conditions linked to frailty (for example, volume

depletion, cognitive impairment, and falls) or conditions overrepresented in frail populations such as lung disease, heart conditions, and elective cataracts.

To account for diabetes severity, we used a modified version [24] of the Diabetes Complications Severity Index (DCSI). This version of the DCSI utilizes ICD-10 codes to produce a 14-level metric, which quantifies the effects of type 2 diabetes on seven different organ systems (Appendix E). It has also been found to be significantly positively associated with the number of hospitalizations over four years, despite not requiring laboratory test results for its calculation [25].

5.3.3 Statistical analysis

We stratified the cohort into three categories based on HFRS. Those with a HFRS of 0 constituted over 50% of the cohort. We considered people with a HFRS in the third and fourth quartile as being frail. This ensured sufficient population sizes within each stratum.

We used Standardized Mean Difference (SMD) to compare differences in baseline characteristics between the treatment and comparator group. SMD was calculated by taking the difference of sample means between the treatment and comparator groups for each covariate and dividing by the square root of the average sample variance of the treatment and comparator groups [26]. SMDs >20% indicated imbalance of the characteristic between groups. We utilized Cox Proportional Hazards Regression with competing risks to estimate the effect between SGLT-2I use versus DPP-4I use against HF hospitalization, MACE, and all-cause death. We

accounted in all three models for clinical differences between people dispensed SGLT-2Is and those dispensed DPP-4Is using Stabilized Inverse Probability Weights (IPW). Stabilized IPWs assigned to those given treatment were calculated by dividing the probability of being assigned to the treatment group divided by the conditional probability of being assigned to the treatment group, given other baseline characteristics. Similarly, the stabilized IPW for those in the comparator group was calculated by dividing the probability of being in the comparator group by the conditional probability of being in the comparator group, given the specific set of baseline covariates [27]. All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

5.4 Results

5.4.1 Cohort characteristics

In total there were 26,913 patients included in the cohort, with 3,132 (11.6%) dispensed SGLT-2Is and 23,781 dispensed DPP-4Is (Table 1). People receiving SGLT-2Is after hospital discharge were younger, with 62.5% being between 30-59 years (38.1% among people who were dispensed DPP-4I). The respective proportions of those in the SGLT-2I and DPP-4I groups aged 80 or over were 0.5% and 5.9%. The proportion of women dispensed SGLT-2Is was 39.3%, and the proportion of women dispensed DPP-4Is was 42.4%.

People in frailty quartiles 1 and 2 all had HFRS scores of 0, collectively these individuals represented 54.9% of the cohort (Table 1). The proportion of people in the fourth frailty quartile was 16.4% among SGLT-2I recipients and 25.2% in DPP-4I recipients. DCSI scores ≥2 were found in 8.9% of DPP-4I recipients and 5.7% of

SGLT-2I recipients. At baseline, people prescribed DPP-4Is, compared to SGLT-2Is, had a higher prevalence of vascular disease (PVD), (3.5% versus 1.8%), hypertension, (36.7% versus 24.9%), HF, (7.6% versus 3.1%), atrial fibrillation (AF), (9.5% versus 4.5%) and stroke, (3.6% versus 2.6%). However, dementia was more prevalent amongst those dispensed SGLT-2Is compared to DPP-4Is (7.7% versus 4.8%). After standardized IPW, the cohort was well balanced (SMD <20%), except hypertension where the SMD was 20.1%.

MACE or HF hospitalization occurred in 3.7% and 1.2% of the SGLT-2I group and 6.6% and 3.6% of the DPP-4I group, respectively, during the one-year follow-up period. 1.1% of the SGLT-2I group and 3.6% of the DPP-4I group died. HF hospitalization and all-cause mortality were particularly low within the fourth frailty quartile among SGLT-2I recipients, with <5 individuals hospitalized for HF and <5 deaths.

Among the entire cohort, the risk of MACE after one year was significantly lower in those initiating SGLT-2Is (HR 0.54; 95%CI 0.44—0.66) compared to those initiating DPP-4Is. SGLT-2I recipients in the third (HR 0.55; 95%CI 0.34—0.87) and fourth (HR 0.45; 95%CI 0.29—0.70) frailty quartiles were also less likely to experience MACE than DPP-4I recipients.

The HF hospitalization risk for the cohort was lower for those receiving SGLT-2Is, compared to DPP-4Is (HR 0.39; 95%CI 0.28—0.54). For those in the third frailty quartile, however, no relationship was observed for HF hospitalization (HR 0.72; 95%CI 0.41—1.29) among SGLT-2I recipients, compared to DPP-4I recipients.

Insufficient outcome numbers prevented meaningful comparison of HF hospitalizations between the two drug groups in the fourth frailty quartile. All-cause mortality (HR 0.52; 95%CI 0.39—0.69) was reduced among the cohort as a whole for individuals dispensed SGLT-2Is compared to DPP-4Is, but not among those in the third HFRS quartile (HR 0.97; 95%CI 0.62—1.53). Due to the low number of deaths amongst individuals prescribed SGLT-2Is in the fourth frailty quartile, all-cause mortality could not be accurately estimated for this stratum.

5.5 Discussion

The main finding of our study was that SGLT-2Is provided similar protection against MACE in people who are frail and non-frail. Our study showed that SGLT-2Is are associated with a 46% reduced risk of MACE compared to DPP-4Is in adults aged ≥30 years. People in the third and fourth frailty quartiles were approximately 50% less likely to experience MACE when dispensed SGLT-2Is compared to DPP-4Is. In people who are frail, SGLT-2Is and DPP-4Is had a similar association with HF hospitalization and all-cause mortality.

Our findings that SGLT-2Is reduce the risk of MI or stroke were consistent with the multi-national CVD-REAL2 study, which showed reduced risk of MI or stroke by 12% and 15%, respectively, compared to DPP-4Is [28]. Additionally, SGLT-2Is were found to reduce the risk of hospitalization for HF by 18-50% in the pooled analysis in the CVD-REAL2 study [29]. Therefore, it is likely that a large part of the risk reduction we estimated for MACE is driven by the inclusion of HF hospitalization in our definition.

We found that both SGLT-2Is and DPP-4Is had a similar association with HF hospitalization in frail populations. Despite similar associations among those in the third frailty quartile with respect to HF hospitalizations, in the overall cohort, SGLT-2Is were associated with a 61% reduced risk of this outcome, compared to DPP-4Is. Our result was within the confidence intervals of Singaporean, Israeli, and Canadian estimates in the CVD-REAL2 study [29]. Conditions that are highly prevalent in frail populations such as prior HF, existing CVD and renal impairment have not been shown to modify the effect of SGLT-2Is on HF hospitalizations [30]. Older age, which is strongly associated with frailty, also is not known to alter the beneficial effects of SGLT-2Is on HF outcomes [31]. The substantial HF hospitalization risk reduction of 82% observed for the fourth frailty quartile was associated with a small number of HF hospitalizations in this frailty stratum and therefore was underpowered to detect a real clinical effect. At the time of this study, SGLT-2Is were relatively new to the Australian market and the beneficial cardiovascular outcomes demonstrated by the Cardiovascular Outcome Trials (CVOTs) were not yet known [1, 2, 32], therefore prescribers may have been more hesitant to prescribe this class of medications to frail individuals. This is demonstrated in our study by the lower prevalence of people with baseline HFRS >1.8 within the SGLT-2I (16.4%) compared to DPP-4I (25.2%) cohorts. These differences were accounted for using IPTWs, which balanced the baseline clinical characteristics of the exposure and comparator groups thus minimizing the effects of prescriber bias.

SGLT-2Is were no less effective than DPP-4Is in preventing all-cause mortality among individuals in the third frailty quartile. This contrasted with the 48% reduction in mortality risk, from SGLT-2Is versus DPP-4Is among the cohort as a whole. The

latter result was similar to a UK study of The Health Improvement Network (THIN) database [33], which estimated that dapagliflozin was associated with half the rate of all-cause death, compared to other antihyperglycemic treatments [33]. It was also similar to the mortality estimates from the CVD-REAL2 [28]. Suissa et al. suggest that some all-cause mortality estimates such as those in CVD-REAL2 may be exaggerated by immortal time bias, resulting from a longer duration of DPP-4I use and possibly a more extended history of type 2 diabetes compared to SGLT-2Is [34]. Within the fourth frailty quartile, the risk estimate associated with SGLT-2Is was unfeasibly low because of the number of SGLT-2I recipients within this stratum who died. This may have been because Australian and international guidelines caution against the intensification of type 2 diabetes regimens for frail individuals and those with important comorbidities or limited life expectancy [7, 8, 35, 36]. It was not possible to ascertain clinicians' perception of poor prognosis from our dataset, but this may constitute an unmeasured confounder that explains the lower incidence of mortality amongst those prescribed SGLT-2Is in the fourth frailty quartile.

5.5.1 Strengths and limitations

This was the first study to examine cardiovascular outcomes and all-cause mortality associated with SGLT-2Is in people who are frail and non-frail. We analyzed data from all Victorian public and private hospitals over a five-year period. Data were available on all reimbursed prescriptions dispensed through community pharmacies and at hospital discharge. Confounding by disease severity was minimized because both SGLT-2Is and DPP-4Is are both second-line agents. We used a treatment decision design [37] rather than an incident user design, and it was possible that

patients used SGLT-2Is or DPP-4Is before their index discharge. This design is relevant to clinical practice because hospital discharge represents a time when clinicians decide to initiate, continue, or discontinue treatment, however results may not be generalizable to individuals who have not been recently hospitalized. Moreover, we could not be sure that individuals identified as being SGLT-2I users during the landmark period did not switch to DPP-4Is during the one-year follow-up and vice versa. The HFRS was originally validated in people aged >75 years and our study population contained patients aged ≥30 years. Data were not available on each patient's glycated hemoglobin, duration of type 2 diabetes, and lifestyle. Finally, we analyzed medication dispensing data and it was not possible to determine if patients dispensed SGLT-2I or DPP-4Is took these medications as prescribed and dispensed.

5.5.2 Conclusion

Our results suggest SGLT-2Is have clear and similar advantages over DPP-4Is with respect to MACE in people who are frail and non-frail. In contrast, SGLT-2Is use have similar effects to DPP-4Is in preventing HF hospitalizations or death in frail people. Our study provides preliminary evidence to suggest that SGLT-2Is may be preferred to DPP-4Is in the treatment of frail people living with type 2 diabetes, which could inform the development of updated type 2 diabetes clinical practice guidelines.

5.6 Tables

Table 1 Baseline Characteristics of Patients Hospitalised with Type 2 Diabetes with a History of Metformin or Sulfonylurea Dispensings in the Year Prior to Index Discharge

	Total N=26,913	**SGLT-2I N=3,132**	**DPP-4I N=23,781**	**Unweighted Standardized Difference (%)**	**Weighted Standardized Difference (%)**
Age, years, (n, %)				-60.1	-9.6
30-59	11,014 (40.9)	1,956 (62.5)	9,058 (38.1)		
60-69	8,916 (33.1)	927 (29.6)	7,989 (33.6)		
70-79	5,572 (20.7)	233 (7.4)	5,339 (22.5)		
80+	1,411 (5.2)	16 (0.5)	1,395 (5.9)		
Sex (n,%)				-6.2	-1.8
Female	11,310 (42.0)	1,232 (39.3)	10,078 (42.4)		
Index discharge year, (n,%)				97.4	10.5
2013	4,566 (17.0)	7 (0.2)	4,559 (19.2)		
2014	6,828 (25.4)	185 (5.9)	6,643 (27.9)		
2015	6,305 (23.4)	674 (21.5)	5,631 (23.7)		
2016	6,130 (22.8)	1,368 (43.7)	4,762 (20.0)		
2017	3,084 (11.5)	898 (28.7)	2,186 (9.2)		
Hospital Frailty Risk Score, (n, %)				-27.6	-8.3
0 (1st and 2nd quartile)	14,762 (54.9)	2,000 (63.9)	12,762 (53.7)		
0.1—1.8 (3rd quartile)	5,633 (20.9)	618 (19.7)	5,015 (21.1)		
>1.8 (4th quartile)	6,518 (24.2)	514 (16.4)	6,004 (25.2)		
Diabetes Complications Severity Index (n,%)				-8.4	2.1
0	21,851	2,568	19,283		

	(81.2)	(82.0)	(81.1)		
1	2,669	386	2,283		
	(9.9)	(12.3)	(9.6)		
≥2	2,393	178	2,215		
	(8.9)	(5.7)	(9.3)		
Medications used up to 1 year prior to discharge (n, %)					
ACE inhibitors/ARB	20,499 (76.2)	2,372 (75.7)	18,127 (76.2)	-1.1	-13.6
Beta-blockers	7,959 (29.6)	805 (25.7)	7,154 (30.1)	-9.8	-3.5
Calcium channel blockers	5,213 (19.4)	481 (15.4)	4,732 (19.9)	-11.9	-6.1
Statin	21,304 (80.0)	2,501 (79.9)	18,803 (79.1)	1.9	-17.2
MRA	1,327 (4.9)	129 (4.1)	1,198 (5.0)	-4.4	4.7
Digoxin	1,098 (4.1)	67 (2.1)	1,031 (4.3)	-12.4	6.6
Diuretics (thiazide & loop)	4,477 (16.6)	284 (9.1)	4,193 (17.6)	-25.4	-6.8
Oral anticoagulant	1,593 (5.9)	77 (2.5)	1,516 (6.4)	-19.1	-0.3
Antiplatelet	6,405 (23.8)	496 (15.8)	5,909 (24.8)	-22.5	-6.9
Antipsychotics	1,269 (4.7)	140 (4.5)	1,129 (4.7)	-1.3	1.6
Medical Conditions Prior to Index Discharge (n,%)					
Unstable Angina	1,209 (4.5)	105 (3.4)	1,104 (4.6)	-6.6	-5.5
Angina pectoris	1,300 (4.8)	113 (3.6)	1,187 (5.0)	-6.8	-8.9
Peripheral vascular disease	895 (3.3)	55 (1.8)	840 (3.5)	-11.1	-9.9
Myocardial infarction	718 (2.7)	86 (2.7)	632 (2.7)	0.5	-2.3
Hypertension	9,499 (35.3)	781 (24.9)	8,718 (36.7)	-25.6	-20.1
Heart failure	1,894 (7.0)	98 (3.1)	1,796 (7.6)	-19.8	3.5
Atrial fibrillation	2,395 (8.9)	140 (4.5)	2,255 (9.5)	-20.0	0.4
Stroke	934 (3.5)	81 (2.6)	853 (3.6)	-5.8	-2.6
Chronic Obstructive	1,268 (4.7)	98 (3.1)	1,170 (4.9)	-9.1	-4.6

Pulmonary Disease					
Cancer	1,914 (7.1)	148 (4.7)	1,766 (7.4)	-11.3	-13.5
Severe hypoglycaemia	77 (0.3)	8 (0.3)	69 (0.3)	-0.7	-3.4
Dialysis	84 (0.3)	3 (0.1)	81 (0.3)	-5.2	-0.3
Chronic kidney disease	4,427 (16.4)	260 (8.3)	4,167 (17.5)	-27.8	-16.6
Diabetic polyneuropathy	1,485 (5.5)	178 (5.7)	1,307 (5.5)	0.8	-1.0
Diabetic eye disease	4,676 (17.4)	430 (13.7)	4,246 (17.9)	-11.3	-2.5
Diabetic foot	1,306 (4.9)	110 (3.5)	1,196 (5.0)	-7.5	-7.8
Other diabetic complications	12,058 (44.8)	1,365 (43.6)	10,693 (45.0)	-2.8	-8.9
Dementia	1,377 (5.1)	240 (7.7)	1,137 (4.8)	12.0	-3.7

Table 2 Risk of Major Adverse Cardiovascular Events, HF hospitalisation and All-Cause Mortality in Patients with Type 2 Diabetes Dispensed Sodium Glucose Cotransporter-2 Inhibitors versus Dipeptidyl Peptidase-4 Inhibitors, Stratified by Frailty Status

Cohort	**MACE HR; 95% CI***	**Heart failure hospitalization HR; 95% CI****	**All-cause mortality HR; 95% CI**
All individuals with T2D ≥30 years, surviving beyond landmark date N=26,913	0.54; 0.44—0.66	0.39; 0.28—0.54	0.52; 0.39—0.69
HFRS = 0 N=14,762	0.60; 0.46—0.78	0.38; 0.22—0.65	0.90; 0.58—1.38
0≤HFRS≤1.8 N=5,633	0.55; 0.34—0.87	0.72; 0.41—1.29	0.97; 0.62—1.53
HFRS> 1.8 N=6,518	0.45; 0.29—0.70	0.18; 0.08—0.40***	0.08; 0.01—0.16****

Cox Proportional Hazards Regression was used with estimates adjusted for variables in Table 6, using Stabilized Inverse Probability Weights; HFRS Hospital Frailty Risk Score
*Competing risk of all non-MACE mortality
**Competing risk of all-cause mortality
*** HR for HF hospitalization is unreliable as <5 individuals prescribed SGLT-2Is in this stratum experienced this event during follow-up.
**** HR for all-cause mortality is unreliable as <5 individuals prescribed SGLT-2Is in this stratum died during follow-up.

5.7 Figures

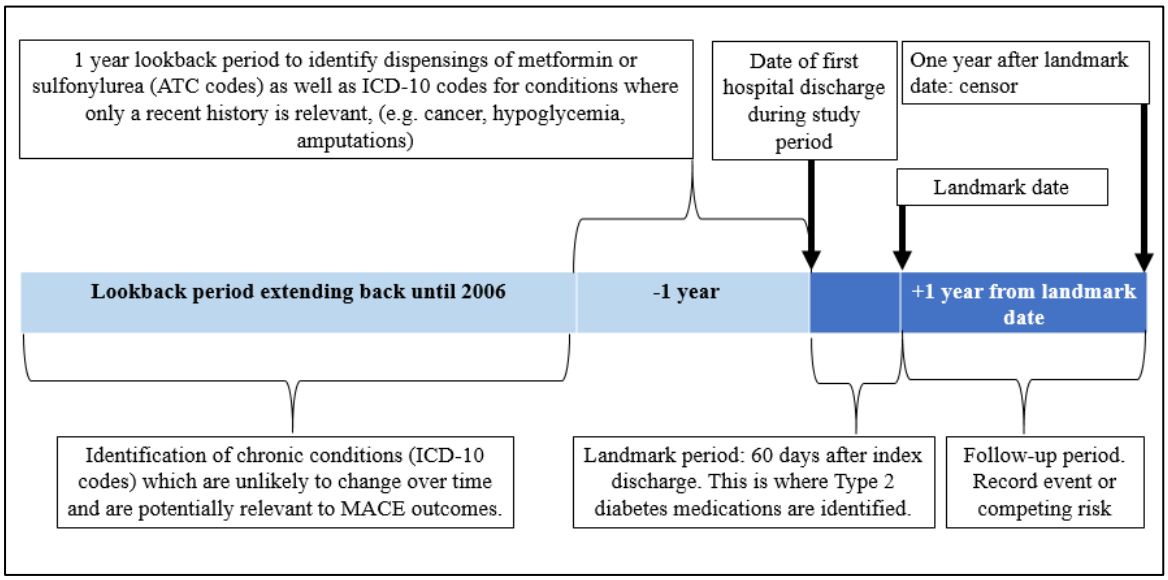

Figure 1: An illustration depicting the study design.

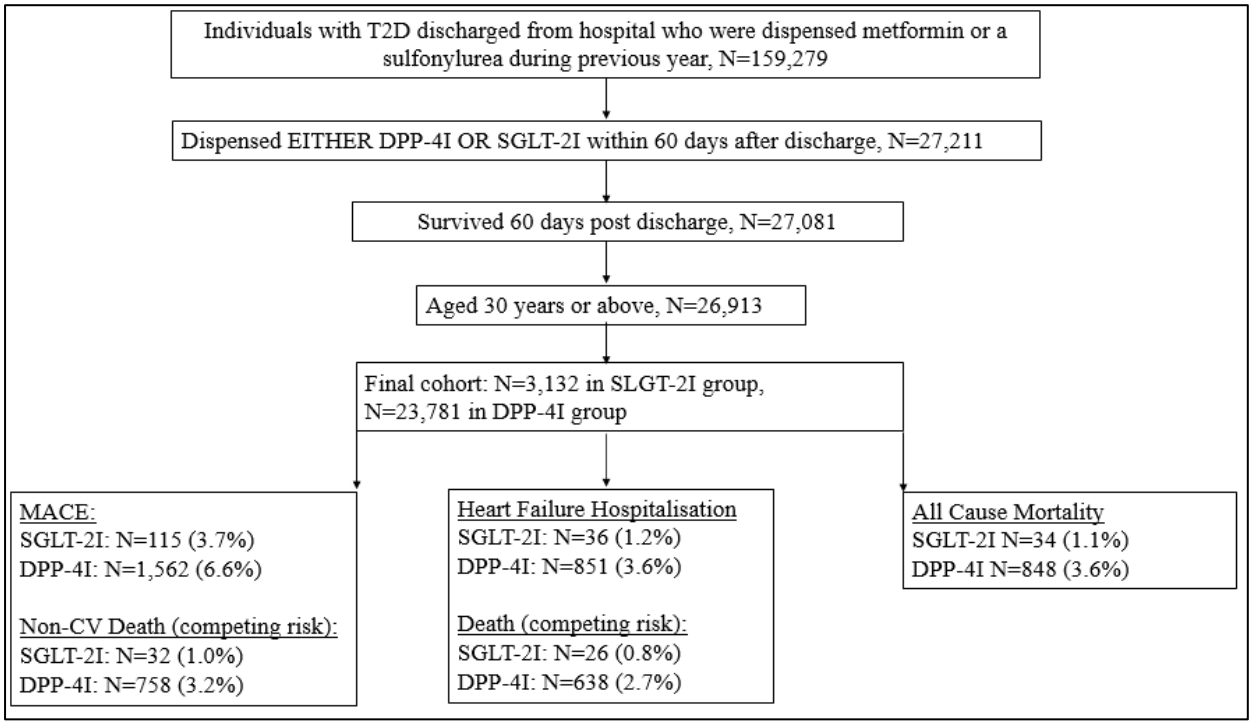

Figure 2: A flowchart indicating how cohort was obtained and numbers of outcomes.

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5.9 Supplementary material

Appendix A: Anatomical Therapeutic Chemical (ATC) codes to identify medications

Drug class	ATC code
Exposure medications	
SGLT-2Is	A10BK (individual), A10BD15-16, A10BD19-21, A10BD23-25 (in combination)
DPP-4Is	A10BH (individual), A10BD10-13, A10BD18-19, A10BD21-22, A10BD24-25 (in combination)
Baseline medications*	
Statin	C10AA, C10BA, C10BX
ACEI/ARB	C09A, C09B, C09C, C09D (exclude C09DX04)
Anti-dementia drugs	N06D
Beta-blockers	C07
Antiplatelets	B01AC
Insulins	A10A
Other lipid-lowering medications	C10AB, C10AC, C10AD, C10AX
Glucose lowering medications	A10A and A10B
Anticoagulant	B01AA
Antipsychotic	N05A
Aldosterone Antagonists	C03DA
Digoxin	C01AA05
Calcium channel blockers	C08C
Loop diuretics and thiazides	C03C (loop diuretics), C03A (thiazides),

SGLT-2I Sodium Glucose Cotransporter-2 Inhibitor; DPP-4I Dipeptidyl Peptidase-4 Inhibitor; ACE Angiotensin Converting Enzyme Inhibitor; ARB Angiotensin 2 Receptor Blocker

* Baseline medications are identified using a fixed one-year period prior to index hospitalization.

Appendix B: Specification of relevant prior medical conditions

Medical condition	ICD-10-AM	Time frame
Thrombolysis	3531701	Full hospitalization history
Angina	I20.0, I20.1, I20.8, I20.9	Full hospitalization history
Hypertension	I10-15	Full hospitalization history
Heart failure	I50	Full hospitalization history
Atrial fibrillation	I48	Full hospitalization history
Stroke	I60-I64	Full hospitalization history
Peripheral artery disease	I70-I73	Full hospitalization history
Chronic kidney disease	E10.2, E11.2, E12.2, E13.2, E14.2, N00-02, N04-08, N11-12, N14-16, N25-28, T82.4, T86.1, Q60- 63, Z94.0, Z99.2, Z49, N17-19	Full hospitalization history
Dementia	F01-F03, G30, U79.1	Full hospitalization history
Dialysis	Z49	Full hospitalization history
Diabetic mono-/polyneuropathy	G99.0, G59.0, G63.2, E10.4, E11.4, E12.4, E13.4, E14.4	Full hospitalization history
Diabetic eye complications	H28.0, H35.8, H36.0, E10.3, E11.3, E12.3, E13.3, E14.3	Full hospitalization history
Diabetic foot/Peripheral angiopathy	E11.6B, M14.2, M14.6, M90.8, L98.4, E10.5, E11.5, E12.5, E13.5, E14.5	Full hospitalization history
Diabetes with several-/unspecified complications	E11.6, E10.6, E13.6, E14.6, E10.7, E11.7, E12.7, E13.7, E14.7, E10.8, E11.8, E12.0, E12.8, E13.8, E14.8	Full hospitalization history
Severe hypoglycemia	E10.0, E11.0, E12.0, E13.0, E14.0, E11.6A, E16.0-2	<I year prior to index date
Keto-/lactate acidosis	E10.1, E11.1, E12.1, E13.1, E14.1, E87.2	<I year prior to index date
Lower limb amputations	Z89	<I year prior to index date
Cancer	C00-C99	<I year prior to index date
COPD and asthma	J44-46	Full hospitalization history
Frailty index*		Calculated on index hospitalization

*Gilbert et al. Lancet 391:1775-1782, 2018

ICD-10-AM International Classification of Diseases (Australian Modified) codes, 10th edition; CVD Cardiovascular disease; COPD Chronic Obstructive Pulmonary Disease

Appendix C: Definition of MACE events

Event	Definition
MI	Hospitalization with a principal diagnosis of MI (ICD10: I21-23)
CABG	Hospitalisation with a procedure code for: 3530400, 3530401, 3850500, 3530500, 3530501, 3531005, 9020100, 3845619, 3865308, 3849700, 3849701, 3849702, 3850003, 3849704, 3849705, 3849706, 3849707, 3850002, 3850004, 3850302, 3850303, 3850304, 3863700, 3850000, 3850001, 3850300, 3850301, 9022100, 9020101, 9020102, 9020103
PCI with Stent	Hospitalisation with a procedure code for: 353100, 3531001, 3531002, 3830600, 3830601, 3830602, 3533800, 3534401, 3831200, 3831201, 3831800, 3831801
Heart Failure	Hospitalization with a principal diagnosis of heart failure (ICD10: I50)
Stroke	Hospitalization with a principal diagnosis of stroke (ICD10: I60-I64)
Revascularization	Hospitalization with a principal diagnosis of revascularization (ICD10: Z95)
CVD death*	Death with any of the above as a primary cause of death

*If a patient died during the follow-up and the primary cause of death was indicated by any of the above ICD-10 codes, then an event was recorded. If the cause of death was not one of the above then a competing risk event was recorded. If no event or competing risk occurred during follow-up then patients were censored after 365 days.

Appendix D: List of 109 ICD-10 codes and number of points awarded for each to create the hospital frailty risk score (HFRS) [21].

ICD Code and Description	HFRS value
F00 Dementia in Alzheimer's disease	7.1
G81 Hemiplegia	4.4
G30 Alzheimer's disease	4.0
I69 Sequelae of cerebrovascular disease (secondary codes)	3.7
R29 Other symptoms and signs involving the nervous and musculoskeletal systems (R29·6 Tendency to fall)	3.6
N39 Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
F05 Delirium, not induced by alcohol and other psychoactive substances	3.2
W19 Unspecified fall	3.2
S00 Superficial injury of head	3.2
R31 Unspecified haematuria	3.0
B96 Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.9
R41 Other symptoms and signs involving cognitive functions and awareness	2.7
R26 Abnormalities of gait and mobility	2.6
I67 Other cerebrovascular diseases	2.6
R56 Convulsions, not elsewhere classified	2.6
R40 Somnolence, stupor and coma	2.5
T83 Complications of genitourinary prosthetic devices, implants and grafts	2.4
S06 Intracranial injury	2.4
S42 Fracture of shoulder and upper arm	2.3
E87 Other disorders of fluid, electrolyte and acidbase balance	2.3
M25 Other joint disorders, not elsewhere classified	2.3
E86 Volume depletion	2.3
R54 Senility	2.2
Z50 Care involving use of rehabilitation procedures	2.1
F03 Unspecified dementia	2.1
W18 Other fall on same level	2.1
Z75 Problems related to medical facilities and other health care	2.0
F01 Vascular dementia	2.0
S80 Superficial injury of lower leg	2.0
L03 Cellulitis	2.0
H54 Blindness and low vision	1.9
E53 Deficiency of other B group vitamins	1.9
Z60 Problems related to social environment	1.8
G20 Parkinson's disease	1.8
R55 Syncope and collapse	1.8
S22 Fracture of rib(s), sternum and thoracic spine	1.8
K59 Other functional intestinal disorders	1.8

N17 Acute renal failure	1.8
L89 Decubitus ulcer	1.7
Z22 Carrier of infectious disease	1.7
B95 Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
L97 Ulcer of lower limb, not elsewhere classified	1.6
R44 Other symptoms and signs involving general sensations and perceptions	1.6
K26 Duodenal ulcer	1.6
I95 Hypotension	1.6
N19 Unspecified renal failure	1.6
A41 Other septicaemia	1.6
Z87 Personal history of other diseases and conditions	1.5
J96 Respiratory failure, not elsewhere classified	1.5
X59 Exposure to unspecified factor	1.5
M19 Other arthrosis	1.5
G40 Epilepsy	1.5
M81 Osteoporosis without pathological fracture	1.4
S72 Fracture of femur	1.4
S32 Fracture of lumbar spine and pelvis	1.4
E16 Other disorders of pancreatic internal secretion	1.4
R94 Abnormal results of function studies	1.4
N18 Chronic renal failure	1.4
R33 Retention of urine	1.3
R69 Unknown and unspecified causes of morbidity	1.3
N28 Other disorders of kidney and ureter, not elsewhere classified	1.3
R32 Unspecified urinary incontinence	1.2
G31 Other degenerative diseases of nervous system, not elsewhere classified	1.2
Y95 Nosocomial condition	1.2
S09 Other and unspecified injuries of head	1.2
R45 Symptoms and signs involving emotional state	1.2
G45 Transient cerebral ischaemic attacks and related syndromes	1.2
Z74 Problems related to care-provider dependency	1.1
M79 Other soft tissue disorders, not elsewhere classified	1.1
W06 Fall involving bed	1.1
S01 Open wound of head	1.1
A04 Other bacterial intestinal infections	1.1
A09 Diarrhoea and gastroenteritis of presumed infectious origin	1.1
J18 Pneumonia, organism unspecified	1.1
J69 Pneumonitis due to solids and liquids	1.0
R47 Speech disturbances, not elsewhere classified	1.0
E55 Vitamin D deficiency	1.0
Z93 Artificial opening status	1.0
R02 Gangrene, not elsewhere classified	1.0
R63 Symptoms and signs concerning food and fluid intake	0.9
H91 Other hearing loss	0.9
W10 Fall on and from stairs and steps	0.9
W01 Fall on same level from slipping, tripping and stumbling	0.9

E05 Thyrotoxicosis [hyperthyroidism]	0.9
M41 Scoliosis	0.9
R13 Dysphagia	0.8
Z99 Dependence on enabling machines and devices	0.8
U80 Agent resistant to penicillin and related antibiotics	0.8
M80 Osteoporosis with pathological fracture	0.8
K92 Other diseases of digestive system	0.8
I63 Cerebral Infarction	0.8
N20 Calculus of kidney and ureter	0.7
F10 Mental and behavioural disorders due to use of alcohol	0.7
Y84 Other medical procedures as the cause of abnormal reaction of the patient	0.7
R00 Abnormalities of heart beat	0.7
J22 Unspecified acute lower respiratory infection	0.7
Z73 Problems related to life-management difficulty	0.6
R79 Other abnormal findings of blood chemistry	0.6
Z91 Personal history of risk-factors, not elsewhere classified	0.5
S51 Open wound of forearm	0.5
F32 Depressive episode	0.5
M48 Spinal stenosis (secondary code only)	0.5
E83 Disorders of mineral metabolism	0.4
M15 Polyarthrosis	0.4
D64 Other anaemias	0.4
L08 Other local infections of skin and subcutaneous tissue	0.4
R11 Nausea and vomiting	0.3
K52 Other noninfective gastroenteritis and colitis	0.3
R50 Fever of unknown origin	0.1

Appendix E: Diabetes Complications and Severity Index (DCSI) scores assigned with relevant ICD-10 codes [22].

DCSI score	ICD-10 Codes	Description of Codes
Ophthalmic		
1	Main Codes	
	E08	Diabetes Mellitus due to underlying conditions
	E09	Drug or chemical induced diabetes mellitus
	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus
	Relevant Subcodes E**.3x, excluding E**.34x & E**.35x	With ophthalmic complications
1	H35.0x	Background retinopathy and retinal vascular changes
1	H35.35x	Cystoid macular degeneration
1	H35.6x	Retinal hemorrhage
	H35.8x	Other specified retinal disorders
	H35.9	Unspecified retinal disorder
2	H33.x	Retinal detachments and breaks
2	E**.34x	Severe nonproliferative diabetic retinopathy Proliferative diabetic retinopathy
2	H54.x	Blindness and low vision
2	H43.1x	Vitreous hemorrhage
Nephropathy		
1	Main Codes	
	E08	Diabetes mellitus due to underlying condition
	E09	Drug or chemical induced diabetes mellitus
	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus
	Relevant Subcodes	With diabetic nephropathy
	E**.21	With diabetic chronic kidney disease
	E**.22	
	E**.29	With other diabetic kidney complication
1	N00.x	Acute nephritic syndrome

1	N04.x	Nephrotic syndrome
1	N03.x	Chronic nephritic syndrome
1	N05.x	Unspecified nephritic syndrome
1	N18.1	CKD, Stage 1
1	N18.2	CKD, Stage 2 (mild)
1	N18.3	CKD, Stage 3 (moderate)
1	N18.9	CKD, unspecified
2	N18.4	CKD, Stage 4 (severe)
2	N18.5	CKD, Stage 5
2	N18.6	End stage renal disease
2	N19	Unspecified kidney failure

Neuropathy

1	<u>Main Codes</u>	
	E08	Diabetes mellitus due to underlying condition
	E09	Drug or chemical induced diabetes mellitus
	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus
	<u>Relevant Subcodes</u> E**.4x	With neurological complications
1	G90.09	Other [than carotid sinus syncope] idiopathic peripheral autonomic neuropathy
1	G90.8; G90.9; G99.0	Other disorders of autonomic nervous system; Disorder of the autonomic nervous system, unspecified; Autonomic neuropathy in diseases classified elsewhere
1	G56.x	Mononeuropathies of upper limb
1	G57.x	Mononeuropathies of lower limb
1	G60.9	Hereditary and idiopathic neuropathy, unspecified
1	G73.3	Myasthenic syndromes in other diseases classified elsewhere
1	G90.01	Carotid sinus syncope
1	H49.x	Paralytic strabismus
1	I95.1	Orthostatic hypotension
1	K31.84	Gastroparesis
1	K59.1	Functional diarrhea
1	N31.9	Neuromuscular dysfunction of

		bladder, unspecified
1	M14.6x	Charcôt's joint
1	S04.x	Injury to cranial nerve
Cerebrovascular		
1	G45.x	Transient cerebral ischemic attacks and related syndromes
2	I61.x	Nontraumatic intracerebral hemorrhage
2	I63.x	Cerebral infarction
2	I65.x	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
2	I66.x	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
2	I67.81	Acute cerebrovascular insufficiency
Cardiovascular		
1	I24.x	Other acute IHD
1	I20.x	Angina pectoris
1	I25.x, excluding I25.2	Chronic ischemic heart disease
1	I70.x, excluding I70.25 & I70.26x	Atherosclerosis
2	I21.x	STEMI and NSTEMI
2	I22.x	Subsequent STEMI and NSTEMI
2	I23.x	Complications following STEMI and NSTEMI
2	I25.2	Old myocardial infarction
2	I48.x	Atrial fibrillation and flutter
2	I46.x	Cardiac arrest
2	I47.x	Paroxysmal tachycardia
2	I49.x	Other cardiac arrhythmias
2	I50.x	Heart failure
2	I70.25/170.26x	Atherosclerosis of native arteries of the extremities with ulceration/gangrene
2	I71.x	Aortic aneurysm/dissection
Peripheral Vascular Disease		
1	<u>Main Codes</u>	
	E08	Diabetes mellitus due to underlying condition
	E09	Drug or chemical induced diabetes mellitus
	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus

	Relevant Subcodes	
	E**.51	Diabetic peripheral angiopathy, no gangrene
	E**.59	Diabetes, other circulatory complications
	E**.621	Diabetic foot ulcer
1	I72.4	Aneurysm of artery of lower extremity
1	I70.21x, I73.89, I73.9	Atherosclerosis of native arteries of extremities with intermittent claudication, Other specified peripheral vascular diseases, Peripheral vascular disease, unspecified
1	S91.3x	Open wound of foot
2	A48.0	Gas gangrene
2	I74.3	Embolism and thrombosis of arteries of the lower extremities
2	L97.x	Non-pressure chronic ulcer of lower limb, not elsewhere classified
2	E**.52	Diabetic peripheral angiopathy, with gangrene
	I96	Gangrene, not elsewhere classified
Metabolic		
1	Main Codes	
	E08	Diabetes mellitus due to underlying condition
	E09	Drug or chemical induced diabetes mellitus
	E10	Type 1 diabetes mellitus
	E11	Type 2 diabetes mellitus
	E13	Other specified diabetes mellitus
	Relevant Subcodes	
	E**.00	With hyperosmolarity, without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
	E**.10	With ketoacidosis, without coma
	E**.649	With hypoglycemia, without coma
2	Main Codes	
	E08	Diabetes mellitus due to underlying condition
	E09	Drug or chemical induced diabetes

	mellitus
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E13	Other specified diabetes mellitus
Relevant Subcodes	With hyperosmolarity, with coma
E**.01	With ketoacidosis, with coma
E**.11	With hypoglycemia, with coma
E**.641	

*The character ‘x’ to the right of a decimal point indicates that 1 or more digits must be added to the main 3 digits to create a billable code.

Chapter 6: Discussion

6.1 Overview

AHAs are important in preventing diabetes complications and death in people with T2D and therefore it is imperative that people with T2D receive guideline recommended AHAs. Chapters 2 through 5 concentrated on a different aspect of AHA utilisation or related health outcomes.

6.1.1 Overview of studies of Australian AHA utilisation

Chapters 2 and 3, taken together, identified important predictors of both initial AHA treatment type, as well as factors that predicted changes to these initial therapies. The overall aims of these first two studies were to:

- Investigate the initial AHA treatments prescribed for people with T2D in Australia and the extent to which factors such as other medication use, age and sex are predictive of the initial AHA therapy prescribed.
- Estimate the rate and extent of therapeutic progression (additions and switches) from initial metformin or sulfonylurea monotherapy, and to identify the predictors of these changes, including age, sex, comorbidities, other medication use and socio-demographic factors.

The study described in Chapter 2 examined the initial AHAs dispensed for people with T2D in Australia, and whether these medications were in line with national prescribing guidelines. Initial AHAs were classified as either metformin monotherapy, sulfonylurea monotherapy, other AHA monotherapy or AHA combinations. Baseline characteristics such as demographic factors and comorbidities, estimated using

medication dispensings, were compared between groups. This study set the foundations for Chapter 3, in which two groups of people with diabetes initiating either metformin monotherapy or sulfonylurea monotherapy were followed up to examine the rate and extent of additions to or switches from initial AHA therapy to a second-line therapy in the year following initiation of the first-line agent.

6.1.2 Overview of studies involving hospitalised patients with T2D

The aims of the hospital-based studies outlined in Chapters 4 and 5 were:

- To determine whether age, frailty, dementia or hypoglycaemia related hospitalisations influence decisions to prescribe less intensive AHA therapies in clinical practice.
- To determine whether SGLT-2Is, compared to DPP-4Is, prevent MACE, HHF and mortality in frail people with type 2 diabetes.

Following the studies investigating the dispensings of AHAs among large samples of Australians with T2D, the studies presented in Chapters 4 and 5 included hospitalised patients with T2D. The study described in Chapter 4 utilised data from Melbourne's Eastern Health hospital network and investigated the predictors of receiving different intensities of diabetes therapies on hospital discharge. The terminology "Glucose Lowering Drug" (GLD) was used in the study as this was the preference of one of the reviewers. The identified categories in ascending order of intensity were "no GLDs," "non-insulin GLDs," "insulin-only GLDs," and "combinations of insulin and non-insulin GLDs." The main predictors explored in this study were age, frailty, dementia status and severe hypoglycaemia, which are all factors outlined in Australian and international diabetes guidelines which should

contribute to the decision to set less intensive glycaemic targets [20, 178]. This study addressed important issues associated with trends in hospital prescribing patterns for older patients with T2D [179].

Chapter 5 outlines a cohort study conducted in the hospital setting, utilising data of individuals aged ≥30 years who were hospitalised with a recorded diagnosis of T2D across all public and private hospitals in the Australian state of Victoria. People who received either SGLT-2Is or DPP-4Is within 60 days after discharge were included. The study population was further stratified by frailty status. The purpose of this research was to determine the effect of SGLT-2Is compared to DPP-4Is on MACE, heart failure and all-cause mortality in people with frailty.

6.2 Discussion of main findings

6.2.1 AHA utilisation patterns

As discussed in Chapter 1, there have been profound changes in the patterns of AHA usage in recent years on a national and international scale [82, 180]. In particular, the uptake of newer agents such as SGLT-2Is, DPP-4Is and GLP-1As has substantially increased, whereas the proportions of sulfonylurea and thiazolidinedione prescribed as an initial treatment have largely declined [82, 139, 180]. As described in Chapter 1, there are similarities between the trends in overall AHA prescribing in Australia and those in the USA [139]. Such trends prompted the question of whether there has been a corresponding increase in the dispensing of newer AHAs as first-line treatments for T2D.

In terms of AHA initiations, a major finding of Chapter 2 was that the first AHA dispensed for most people between 2013 and 2018 was metformin (86%). There were also a minority of individuals who were dispensed sulfonylurea monotherapy (5%). This finding was largely in accordance with Australian general practice diabetes guidelines, which recommend metformin monotherapy as an initial AHA but also advise that sulfonylurea monotherapy can be prescribed where metformin is contraindicated [20]. These results were also in line with those from a multinational study of AHA dispensings in Spain, Italy, France, the UK and the Netherlands, which estimated that between 65% and 88% of people receiving initial treatments for T2D received metformin monotherapy [181]. The same study also estimated that the proportion of sulfonylurea monotherapy initiations ranged from approximately 4% to 14% across the five European countries between 2008 to 2012 [181]. Real world data from the USA indicate that between 2005 and 2016, the proportion of AHA initiations involving metformin increased from 60% to 77%, whereas the proportion of sulfonylurea initiations decreased over the same period from 20% to 8% [139]. The lower proportion of initiations involving metformin in the USA study may be partially explained by the inclusion of insulin, which was prescribed for between 8% and 10% of the population, as a possible first-line agent [139]. The methodology used in Chapter 2 assumed that people initiating on insulin as a first line AHA would have done so because of a T1D diagnosis. Therefore, to prevent misclassification, insulin was not considered as a possible first-line AHA for T2D.

In Chapter 2, it was found that initiations with non-guideline monotherapy were 35% more likely in 2017/18 (OR 1.35; 95%CI [1.09—1.67]), compared to 2013/14. According to our sensitivity analyses, this was largely driven by increases in use of

SGLT-2I monotherapy being prescribed as initial therapy. In parallel with this, the odds of sulfonylurea monotherapy being prescribed as an initial T2D therapy significantly decreased with every year of the study and was only half as likely to occur in 2017/18 (OR 0.48; 95%CI [0.41—0.57]), compared to 2013/14.

Australian guidelines do not discuss initial therapy with >1 AHA, regardless of HbA_{1C} [20]. Nevertheless, in Chapter 2, we estimated that approximately 8% of initial T2D therapies involved >1 AHA. Similarly, a 2014 study in an Australian veteran population found that approximately 22% of metformin and glibenclamide combination recipients had no record of use of either of these agents as monotherapy [182]. The AACE and American College of Endocrinology (ACE) recommend the initiation of dual therapy if HbA_{1C} > 58 mmol/mol (7.5%) [183, 184], whereas the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend initial dual therapy if HbA_{1C} ≥ 75 mmol/mol (9.0%) [184]. Although such prescribing is not consistent with the requirements necessary to attract a PBS subsidy in Australia, there remains some contention about the possible benefits of initial combination therapy [134]. Possible advantages of initial combination therapy include a reduced “legacy effect,” avoidance of potential clinical inertia and preservation of pancreatic β-cell functionality [185]. Furthermore, a meta-analysis found that attaining HbA_{1C} < 53 mmol/mol (7.0%) using initial combination therapy is 40% more likely compared to initial metformin monotherapy [186]. A study by Olansky et al. also showed that initial use of sitagliptin/metformin, rather than metformin alone, increased the likelihood of attaining HbA_{1C} < 48 mmol/mol (6.5%) by 70% [187]. Nevertheless, initial combination therapy has potential disadvantages compared to initiation with

monotherapy, including a higher probability of adverse events and potentially lowering HbA_{1C} too rapidly [134]. Australian Guidelines caution against overly aggressive treatment targets among people with “important comorbidities” or “established vascular complications.” The former recommendation may explain why the odds of receiving initial combination therapy estimated in Chapter 2 were 64% lower for people with 7+ comorbidities, compared to those with none.

In Chapter 3, the rates of addition to, or switching from metformin or sulfonylurea monotherapy were estimated using a retrospective cohort study design with a follow up period of one year. It was found that 28% of sulfonylurea initiators and 18% of metformin initiators had another AHA added to their initial therapy. Furthermore, 13% of sulfonylurea initiators and 4% of metformin initiators had their initial AHA switched. In total, approximately 23% of the cohort received either an addition or a switch within one year. This result was similar to an Australian study conducted in 2010 in a veteran population by Vitry et al., which reported that about 24% of new users of sulfonylureas or metformin had their T2D treatment progressed after one year [135]. Like Vitry et al., the study in Chapter 3 demonstrated an inverse relationship between increasing numbers of comorbidities and risk of AHA treatment progression. For instance, the risk of addition to metformin therapy was 21% lower for people with ≥5 comorbidities versus none, while the sulfonylurea initiators with ≥5 comorbidities versus no comorbidities were 44% less likely to receive an AHA addition. A point of difference of Chapter 3 was that switches were distinguished from additions. Because of this distinction, we were able to identify that switching was 24% more likely in metformin initiators with ≥5 comorbidities compared to those without comorbidities. Older age reduced the risk of AHA additions among both sulfonylurea

and metformin initiators, which is likely to reflect the setting of more conservative glycaemic targets among older individuals [20].

With respect to medical conditions, people with CHF had a higher risk of receiving add-on therapy, regardless of whether they initiated metformin or a sulfonylurea. This may be because co-existing T2D and CHF are associated with substantially increased mortality compared to either condition alone [188] and a 25% increased risk of cardiovascular death or HHF over three years, for every 1% increase in HbA_{1C} level [189]. People who received metformin and were attempting smoking cessation were 32% more likely to receive an additional AHA. Lycett et al. found smoking cessation was an independent predictor of deterioration in glycaemic control, which persists for three years [190]. This may be due in part to overeating after smoking cessation. This may explain the higher rate of addition of AHAs among individuals dispensed smoking cessation products. In addition, it may indicate more intensive diabetes management in people who smoke.

Another finding of the study described in Chapter 3 was that people living in Australia's most remote locations (Accessibility-Remoteness Index of Australia [ARIA] scores 4-5) who initiated metformin were less likely to have this medication switched than those living in major cities. This finding was of potential concern since it is known that diabetes mortality rates are approximately 54% higher in outer regional and remote areas, compared to major cities [191]. Our multivariate model was adjusted for socioeconomic disadvantage (Socio-Economic Indexes for Areas [SEIFA] scores) as well as for Aboriginal or Torres Strait Islander status, but these did not change the significance or magnitude of the relationship. Although lower

rates of switching from metformin in remote areas could indicate reduced opportunities for follow-up or reduced access to specialist T2D care compared to major cities [38], it could also be that people in remote locations are simply more likely to tolerate mild adverse effects from metformin. Considering the small overall number of people switching from metformin and the fact that people in remote locations were not less likely than those in major cities to receive additions to metformin, we could not unequivocally state that this finding is indicative of suboptimal care.

The study described in Chapter 3 also identified that time to AHA addition was associated with the time between T2D diagnosis and the initiation of the first AHA, (either metformin or sulfonylurea). Compared to individuals dispensed their first AHA on their diagnosis date, people with time intervals up to 2 years between T2D diagnosis and first AHA had progressively longer times to second-line medication add-on. The most likely explanation is that individuals whose T2D followed a less aggressive course would have been likely to experience longer time intervals between diagnosis and AHA initiation, as well as a longer time interval before an additional AHA was needed. Clinical inertia, which is described in Chapter 1 [192], could be a secondary explanation for this, as prescribers who take longer to prescribe initial therapy may also take longer to initiate further therapies. Potential contributors to clinical inertia include prescribers' resistance to prescribing new medications and concerns about medication costs. Delaying the addition of a second AHA, when indicated, has well established disadvantages. Desai et al. report that people taking metformin or sulfonylurea with HbA_{1C} ≥7.0% (53mmol/mol), who received an additional AHA between 1-2 years were 22% less likely to achieve

glycaemic targets during the 7-year follow-up compared with those who received one within 12 months [141].

Finally, the median time between T2D diagnosis and treatment initiation was longer for people in the sulfonylurea cohort than for those in the metformin cohort. Since sulfonylurea initiators were older than metformin initiators, this is consistent with a study by Zhang et al., which found that people aged ≥65 years had significantly longer time intervals between T2D diagnosis and AHA initiation than for those aged <65 years [193].

6.2.2 Discussion of results from studies involving hospitalised patients with T2D

The key finding of Chapter 4 was that both age and frailty are independent predictors of clinicians prescribing less intensive AHA therapies in older people with T2D and a diabetes related complication. For example, combinations of insulin plus other AHAs were 63% less likely to be prescribed for people ≥80 years than for those between 65 to 80 years, compared to no AHAs. Furthermore, people classified as most frail were 35% less likely than non-frail individuals to be prescribed combinations of insulin plus other AHAs, compared to no AHAs.

The results of Chapter 4 highlight that prescribers recognise the importance of avoiding overly intensive glycaemic therapy in both older people and people who are frail, which is in line with best practice recommendations. National and international prescribing guidelines advise that people with limited life expectancy do not gain substantial benefits from more stringent glycaemic targets and indeed such targets

may result in harm [20, 149]. It is well established that overtreatment of T2D among older people and those living with frailty contributes to adverse outcomes such as hypoglycaemia, falls, hospitalisation and mortality [194-196]. Furthermore, sarcopenia and weight loss resulting from frailty can be accelerated and exacerbated by the shift in the natural history of diabetes from a progressive to a regressive course ("burn-out diabetes") [17].

Older people with T2D are less likely to recognise early warning signs of hypoglycaemia and also have slower reaction times than their younger counterparts [197]. The consequences of severe hypoglycaemia can be significant, including sudden cardiovascular death, and even mild hypoglycaemia can lead to falls, bone fractures, seizures, coma, cardiovascular events and cognitive impairment [194]. A study from the USA indicates that the incidence of hospitalisation for hypoglycaemia in insulin users >80 years is five times that of insulin users aged 45-64 years [198]. It is thought that reduced food intake and administration of incorrect insulin products contribute to this increased risk [198].

There are reciprocal relationships between diabetes, frailty and dementia, which are largely attributable to hypoglycaemia [199]. Our study was underpowered to detect significant differences in the likelihood of people with dementia receiving more intensive AHAs at hospital discharge; however, there was a trend towards people with dementia having lower odds of receiving combinations of insulin and other AHAs. This may reflect prescribers' awareness of the need to reduce the complexity of T2D regimens and to minimise insulin usage, where possible, among older people with dementia. Without assistance, it is unlikely that people with dementia would

manage complex AHA regimens successfully, with difficulties in remembering dosage directions and whether to take the insulin with or without food being particularly problematic [200].

With respect to the secondary aim of Chapter 4, we found that people hospitalised with severe hypoglycaemia were four times as likely to be prescribed an insulin-only regimen and three times as likely to receive insulin and non-insulin combinations, compared to no AHAs. Moreover, of those in the insulin plus non-insulin AHA group, 16.5% of patients were prescribed at least two insulin products. Simplification of regimens involving multiple insulins to basal insulin glargine only, can reduce the total duration of hypoglycaemic episodes by 65% [201]. Without data on HbA_{1C}, we were unable to ascertain whether such prescribing was appropriate, however, it is clear that there may be some scope to deprescribe or simplify insulin therapy within this subgroup of older people.

In Chapter 5, the main finding was that SGLT-2Is reduced the risk of MACE to a similar extent (~50% reduction) in people with no frailty (HFRS frailty scores of zero) as well as in people in the third and fourth frailty quartiles, compared to DPP-4Is. This suggests that SGLT-2Is provide similar protection against MACE in people who are frail and non-frail.

Overall, SGLT-2Is were associated with 46% reduced risk of MACE compared to DPP-4Is in adults aged ≥30 years. This result was more pronounced than but directionally consistent with the CVD-REAL2 study, which estimated that SGLT-2Is, compared to DPP-4Is, reduce the risk of MI or stroke by 12% and 15%, respectively

[202]. The more substantial risk reduction observed in Chapter 5 is likely to have been driven by our inclusion of HHF in our MACE definition, as SGLT-2Is have been shown to have more substantial effects on this outcome compared to other cardiovascular outcomes [165, 202].

We found that the risk of HHF was 61% lower for people dispensed SGLT-2Is compared to DPP-4Is, which was within the confidence limits of estimates from Singapore, Israel and Canada in the CVD-REAL2 study [165]. Older age, prior heart failure, existing CVD and renal impairment have not been shown to modify the effect of SGLT-2Is on heart failure outcomes [203, 204]. Therefore, we expected that people with higher levels of frailty, which is strongly associated with all of these characteristics, would have similar reductions in HHF risk as non-frail people. However, the results of Chapter 5 showed that the protection against HHF conferred by SGLT-2Is was not significantly different to DPP-4Is among people with diabetes in the third frailty quartile, compared to those without frailty.

We were unable to reliably estimate the risks of all-cause mortality and HHF in the fourth frailty quartile in our study because the number of these outcomes within this stratum were too low (N=3 and N=2), respectively, and therefore underpowered to provide reliable indications. There were only 514 individuals in the fourth frailty quartile who received SGLT-2Is and part of the reason for this low number may be that there was a level of prescriber bias. As previously discussed, Australian and international guidelines advise avoidance of T2D treatment intensification for people with important comorbidities or limited life expectancies [51, 129, 183, 184]. Hence, clinicians' perception of poor prognosis may have made the prescribing of SGLT-2Is,

rather than DPP-4Is less likely. Furthermore, for most of the duration of this study, the CVOT results regarding cardiovascular benefits associated with SGLT-2Is [87, 123, 205], were unknown. This may have made the prescribing of a new class of medication to individuals with very high frailty levels and severely reduced life expectancies less likely. Indeed, the table of baseline characteristics associated with this chapter (Chapter 5, Table 1) shows there were lower proportions of people with baseline HFRSs >1.8 within the SGLT-2I (16.4%) compared to DPP-4I (25.2%) cohorts.

Overall, the cohort of Chapter 5 had a 50% reduced risk of all-cause mortality in people who received SGLT-2Is rather than DPP-4Is. The CVD REAL2 study estimated a similar relative risk of all-cause mortality (RR 0.51; 95%CI [0.37—0.70]). A UK cohort study of The Health Improvement Network (THIN) database [142], which used only dapagliflozin as an exposure, and all other AHAs as comparator treatments, also estimated a 50% decreased risk of all-cause mortality. Individuals in the third quartile of frailty of our study, in contrast, did not have significantly lower risks of all-cause mortality with SGLT-2Is versus DPP-4Is.

6.3 Methodological strengths and limitations

Selection bias, information bias and confounding, as well as the role of chance are almost inevitable limitations of observational studies [170, 206]. In this section, these factors, as well as the external validity or generalisability, of the results are discussed.

6.3.1 Selection bias

With respect to selection of individuals, the databases described in Chapters 2 and 3, avoided volunteer bias as there was no requirement to obtain consent to participate. There was a broad national coverage of all PBS-subsidised AHA dispensings in Chapter 2 and sampling of the 10% of people eligible for PBS subsidy was random. Furthermore, death dates were available using data from the National Death Index (NDI) provided by Australian Births, Death and Marriages Registry. Despite this, there were also some potential limitations in terms of selection. In Chapter 2, the PBS 10% dataset lacked a variable to indicate diagnosed T2D, therefore, individuals were included on the basis of being dispensed an AHA. However, metformin is used in the treatment of polycystic ovarian syndrome in premenopausal women, therefore the proportion of younger women with T2D initiating metformin may have been overestimated. A UK study has shown that the proportion of women over 40 years prescribed metformin for this indication is relatively low [207]. For this reason, we only included individuals aged 40 years and over in Chapter 2. A further issue contributing to selection bias in Chapter 2 was the decision to exclude individuals who had been prescribed insulin as an initial AHA. This decision was necessary to avoid inclusion of people with T1D, and it has previously been shown in surveillance studies that the prescribing of insulin as an initial treatment for T2D is uncommon [208]. It is also possible that a subset of people taking AHAs which were not PBS subsidised and therefore such dispensings would not be included in the PBS dataset. The higher cost likely to be incurred by patients from receiving unsubsidised AHAs would, however, mean that this would likely be rare. Furthermore, a small number of individuals included in Chapters 2 and 3 who emigrated from Australia, would have been lost to follow-up. Finally, the

dataset does not capture all prescriptions for AHAs, but rather, only those which have been dispensed. Hence, there would be a proportion of undispensed prescriptions which would not have been included in the dataset.

In Chapter 3, the linked NDSS-PBS dataset provided an excellent coverage of at least 85% of people in Australia diagnosed with T2D, as well as the other advantages described previously associated with the PBS dataset. Some selection bias may have resulted from the absence of <15% of Australians with diabetes who did not enrol in the NDSS, and it is possible that this subgroup may have been systematically different. It is also possible that the variable used to identify diabetes "type" in the NDSS dataset, could have also resulted in some level of misclassification as a result of transcriptional or diagnostic errors from clinicians. This variable is often associated with a degree of uncertainty because identification of T1D or T2D is often made in the early stages of diabetes treatment when a precise diagnosis may be unclear [209].

The hospital-based studies described in Chapters 4 and 5 permitted selection of a large number of hospitalised patients with T2D and like the studies in Chapters 2 and 3, were not limited by volunteer bias. In Chapter 4, there was coverage of 3 acute and 4 subacute hospitals, (1,423 beds), across the EH hospital network in Melbourne's Eastern suburbs, with 1,175,249 episodes of care between July 2015 and June 2016 [173, 175]. The breadth of data provided by the linked VAED-PBS dataset was considerably more substantial, with all public and private hospitals across the Australian state of Victoria being included. Victoria is Australia's second most populated state with a population of 6.7 million. The cohort selected for Chapter

4 consisted of patients 65 years and over, hospitalised with an ICD-10 code indicative of T2D as well as at least one diabetes-related complication. This was not so much a bias as a restriction to the study population, which was specified upfront; however, it does restrict the population to which the results may be generalisable. Similarly, Chapter 5 included only patients aged ≥30 years, hospitalised with an ICD-10 code indicative of T2D and a one-year history of either a metformin or sulfonylurea dispensing. We did not exclude patients with a history of insulin use so we could not be sure that all selected individuals were at a comparable stage in the diabetes treatment pathway. After discharge, we utilised a 60 day "landmark period" during which we identified SGLT-2I or DPP-4I dispensings. It is possible that some individuals may have had stockpiled SGLT-2Is or DPP-4Is from prior to their first hospitalisation and therefore, did not need to receive a dispensing during the landmark period. Such individuals would have not been included in the analysis.

Finally, for Chapter 5, the treatment decision design [210] was chosen, rather than an incident user design, therefore, patients may have used SGLT-2Is or DPP-4Is before their index date. Patient discharge from hospital is a time when clinicians can initiate, continue, or discontinue treatment, so the use of this design provides an accurate indication of clinical practice procedures and treatment decisions in hospital settings. It also enabled a broader selection of patients prescribed SGLT-2Is to be included in the study.

6.3.2 Information bias

Administrative datasets such as those used in Chapters 2 and 3 have many strengths for example large population sizes and systematic data collection over time

[211]. It has been suggested that administrative datasets are likely to be the best source of information for epidemiological studies investigating the prevalence and incidence of diseases [211]. Since 1st of July 2012, the PBS 10% dataset has been a particularly rich source of information about AHA dispensing in Australia because all PBS dispensings of AHAs have been captured. Prior to this date, only government subsidised general and concessional prescriptions were included in the dataset, while general items costing less than the co-payment threshold, were not. Thus, a substantial proportion of lower-priced AHAs such as metformin and sulfonylureas, which were below the threshold cost for government co-payment, would have been absent. For this reason, all studies involving PBS data were conducted after 1st of July 2012. One limitation concerning Chapter 2 was that the PBS 10% dataset did not include hospital inpatient dispensings. Hence, AHA initiations for hospital inpatients would not have been captured if they were different to those AHAs dispensed on discharge. It was reasoned that this was unlikely to be a significant concern because the medication initiated in the hospital setting was likely to have been subsequently dispensed via the PBS either at patient discharge or in the community setting.

A common limitation across all studies was the inherent lack of information about whether people receiving AHAs actually used them as prescribed. Adherence to prescriber directions is also affected by the type of AHA prescribed, with a systematic review and meta-analysis of 48 studies showing that sulfonylureas, thiazolidinediones and DPP-4-Is are all associated with higher levels of adherence than metformin [212]. The same review also found that rates of non-persistence were twice as great among GLP-1RAs compared to long-acting insulin analogues [212].

It is impossible to distinguish whether apparent cessation of a medication was prescriber or patient initiated. This was made more challenging by the lack of information about dosage directions. This was a prominent limitation in Chapter 3, since metformin and sulfonylureas are available in multiple pack sizes in Australia, and can be taken at various dosages, therefore it was difficult to distinguish switches from additions. To address this, we conducted a sensitivity analysis with a longer grace period than the main analysis, which resulted in fewer identified episodes of initial AHA cessation and consequently a small number of switches being reclassified as additions.

The Rx risk index [213] provided markers of diseases or conditions, based on ATC codes for dispensed medications, which were used as outcome predictors in Chapters 2 and 3. This method is a less sensitive and specific indicator of medical conditions and comorbidity scores, compared to ICD-10 codes which are specific to diseases recorded by a medical doctor. For example, “nicotine dependence” was indicated by the dispensing of varenicline or nicotine replacement therapy. However, individuals who are nicotine dependent may be current smokers or could be attempting to cease smoking with or without the aid of over-the-counter products which are not PBS subsidised. Therefore the “nicotine dependence” marker of the Rx-Risk index is unlikely to be highly sensitive. Similarly, the Rx-risk category indicating CHF was based upon receipt of β-blockers and loop diuretics, however, these medications are prescribed for other conditions such as hypertension and oedema, respectively, so it is possible that some people were misclassified as having CHF. In Chapter 3, the duration of time between T2D diagnosis and initiation

of AHA therapy was used as a predictor of treatment change. This variable was problematic because some diagnoses occurred prior to 1st July 2012, before which date general prescriptions for metformin and sulfonylureas, which generally cost less than the government co-payment threshold, were absent from general PBS data collection. To overcome this, we conducted a sensitivity analysis using only concessional prescription dispensings, all of which were included in the PBS dataset. A further limitation of the NDSS dataset was that Aboriginal or Torres Strait Islander Australians are able to access medications through avenues such as the Remote Area Aboriginal Health Services Program. Thus, not all of these individuals' dispensed medications would appear in the PBS dataset [148].

In the hospital-based studies described in Chapters 4 and 5, information bias could have resulted from a lack of accuracy in clinical coding on the part of hospital-based coding staff, or the use of different coding criteria across time and between institutions [211]. It has been shown that coding accuracy can be affected by the data source, medical condition, or procedure, as well as the disease definition [214]. We also identified patient comorbidities in Chapter 5 based upon diagnosis codes only, however, procedural codes combined with diagnosis codes are slightly more sensitive and selective than diagnosis codes alone [214, 215]. The linkage of large datasets such as the different EH sites and the VAED to the PBS is a time consuming and labour-intensive undertaking, which can result in delays in access and possible incorrect matching resulting from probabilistic methodology. The probabilistic matching for database in Chapter 5 was performed by the Australian Institute of Health and Welfare with >85% of all eligible records being linked. Records of previously dispensed medications were available in Chapter 5, due to the

linkage to the PBS, however, only medications prescribed at the point of hospital discharge were available in Chapter 4.

Two derived variables used in Chapters 4 and 5 were the Diabetes Complications Severity Index (DCSI) [216] and the Hospital Frailty Risk Score (HFRS) [161]. The original DCSI was validated in 2008 and was found to be better than comorbidity scores in predicting hospitalisations and mortality in people with diabetes [217]. The DCSI used in this PhD project was an updated version of the 2008 DCSI and used ICD-10 rather than ICD-9 codes. It was derived from a fourteen-level metric based upon ICD-10 codes indicative of complications within seven different physiological systems [216]. Despite the differences in its calculation, the modified version of the DCSI has been shown to be a suitable substitute for the previous version [216]. The HFRS has been validated in hospitalised patients 75 years and over and was described in detail in Chapters 4 and 5. A limitation of the application of the HFRS is that we applied to populations ≥65 years and ≥30 years in Chapters 4 and 5 respectively.

One further source of information bias which may be present in the study reported in Chapter 5 was immortal time bias [218]. This type of bias arises when people receive a relevant treatment prior to commencement of a study, for a period of time which is not recorded as follow-up time. This would have been a source of bias because it is likely there would have been more individuals taking DPP-4Is, possibly for up to a decade, prior to study commencement and this period would not have been recorded. One method used to address immortal time bias in Chapter 5 was to utilize a landmark period lasting for 60 days after the index discharge date [219]. Only

individuals who survived this period were included in the analysis, in order to minimise the effects of differential mortality between the DPP-4I and SGLT-2I groups during the period immediately after discharge.

6.3.3 Confounding

In observational studies, a confounder is a third variable which is associated with the exposure and predicts the outcome. This variable can distort the relationship between the exposure and outcome [220]. In Chapters 2 through 5, the selection of confounders was based upon the clinical opinions of the authors as to the factors likely to influence either prescribers' treatment selection or prognosis following treatment initiation. There was no "gold standard" in terms of the exact confounders used in the adjusted models and many relevant confounders may have been unavailable or unmeasurable. Some confounders which would have been potentially informative, but were absent from all datasets were renal function, HbA_{1C}, BMI, smoking status and alcohol consumption.

An example of confounding in Chapter 2 was apparent from the fact that older people were less likely to be supplied with initial combination therapy than those who were younger. This relationship may have been confounded because older people have more comorbidities and more contact with GPs to manage these conditions. Therefore, older people, compared to younger people, may have been diagnosed at an earlier stage of their T2D when their HbA_{1C} would have been less elevated than if GP contact was delayed (Figure 6).

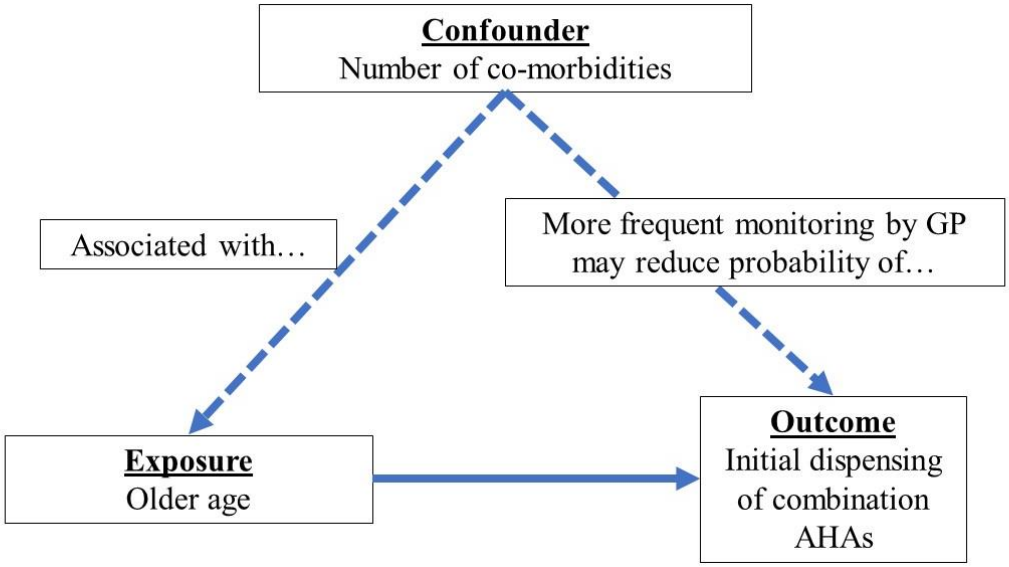

Figure 6: An illustration depicting how number of co-morbidities may confound the relationship between older age and the dispensing of initial combination AHA therapy

Likewise, in Chapter 3, people initiating metformin with ≥5 comorbidities, compared to none, were 24% more likely to receive an AHA switch. This may be partially attributable to confounding among those with ≥5 comorbidities, due to the presence of a higher proportion of people with severe renal impairment in this category [221].

In Chapter 4 the availability of ICD-10 codes indicative of diagnoses enabled more granular identification of comorbidities than the Rx-risk tool used in Chapters 2 and 3. Using Variance Inflation Factors (VIF) with a cut-off of 2, we noted that there was a high degree of collinearity between various cardiovascular diseases, such as MI and heart failure, and concomitant cardiovascular medications. Therefore, we excluded the individual cardiovascular medications from our final multivariate model. We conceptualised concomitant cardiovascular medications (such as statins, ACEIs, β-blockers and calcium channel blockers) as being intermediate variables in the causal pathway between cardiovascular diseases and the type of AHAs prescribed (Figure 7). We reasoned that some concomitant medications would be more of a

marker for cardiovascular events or cardiovascular disease, rather than appropriate predictors of AHA therapies in their own right.

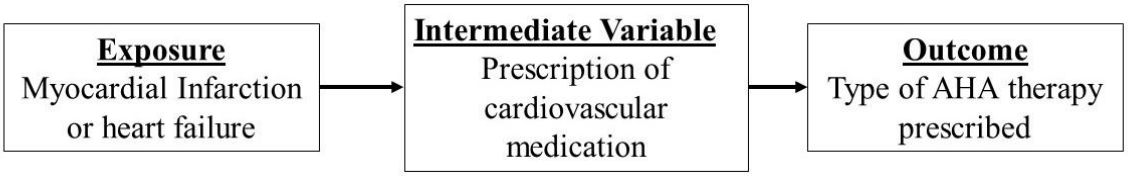

Figure 7: An illustration depicting cardiovascular medications as intermediate variables in the causal pathway between prior myocardial infarction and type of AHA received.

In Chapter 5, we partially addressed confounding by indication by selecting a comparison group (DPP4-I) to be as similar as possible for patient characteristics as the exposure group (SGLT2-I). However, some differences in the baseline characteristics of people prescribed SGLT-2I and DPP-4Is remained. Since SGLT-2Is were relatively new to the Australian market during this study period, it was hypothesised that these agents would be less likely to be prescribed to more vulnerable or seriously unwell people with T2D. If left unaddressed this confounding could lead to overestimations of the benefits of SGLT-2Is, as recipients would have been less likely to experience cardiovascular events or to die (Figure 8). We used stabilised Inverse Probability Weights (IPWs) [222] to balance for measured confounders between the SGLT-2I and DPP-4I cohorts because this has been shown to be superior to propensity score matching in research involving comparative effectiveness [223]. IPWs are described in detail in Chapter 5 but an important advantage of this method compared to propensity score matching is that all eligible individuals are included in the final analysis [224].

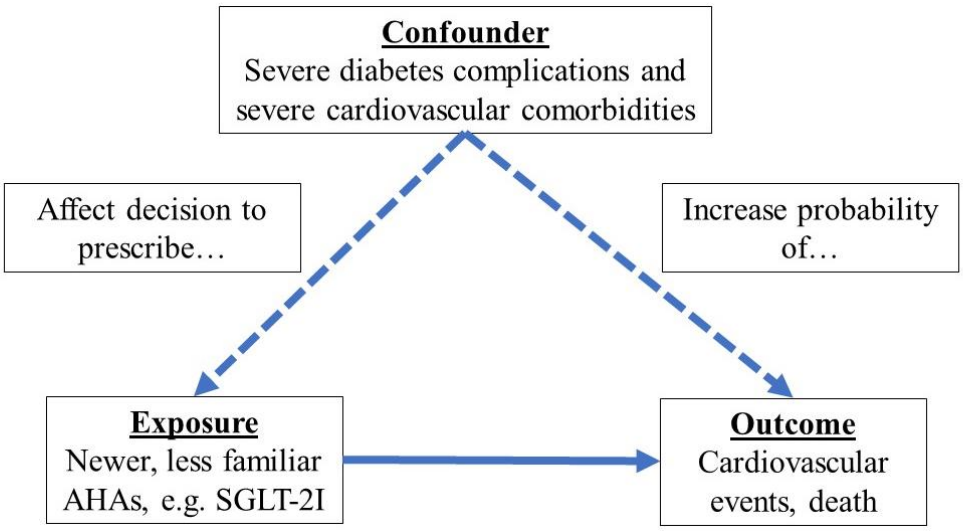

Figure 8: An illustration depicting confounding by disease severity, and how this can distort the relationship between exposure and outcome.

6.4 Implications and future research directions

From a policy and surveillance perspective, Chapter 2 provides reassurance that clinicians generally adhere to clinical guidelines, with regards to AHA initiation, but also indicates that combination therapy whilst not guideline-recommended in Australia, still occurs in a minority of people with T2D. Further studies on the initial use of >1 AHA upon T2D diagnosis as opposed to stepwise treatment progression could be considered since there is clear evidence of the harms of delays in achieving glycaemic targets [29]. It is also likely that subsequent to the completion of this study, the uptake of SGLT-2Is as initial AHAs could have considerably increased, and current ADA guidelines recommend their initiation in people with CHF [62]. Hence it is reasonable to suggest that a study comparing the outcomes from prescribing metformin versus SGLT-2I as an initial AHA could be conducted. It remains to be seen whether improved clinical outcomes alone would be sufficient to warrant a change in recommended first line agents as it may not be economically feasible due to the greater expense of SGLT-2Is compared to metformin. Chapter 2

also suggests that people with CHF are less likely to receive metformin compared to sulfonylureas as an initial agent. This is despite sulfonylureas being more harmful than metformin in terms of cardiovascular and hypoglycaemic events [225, 226]. Education programs may be necessary to discourage initial prescribing of sulfonylureas in the absence of severe renal disease.

Relating to Chapter 3, although we were unable to identify definitive instances suboptimal prescribing based on ARIA scores, the observation that metformin switches were less likely to occur in Australia's most remote locations may warrant further investigation. It is already known that GPs practising in rural and remote Australia face challenges in accessing diabetes specialists and diabetes educators [38]. People in remote areas also have 40% increased odds of having suboptimal HbA_{1C} levels, compared to people in inner regional areas [227]. Moreover, people with diabetes in Australia's most remote areas are more likely to receive older AHAs than those in major cities [148]. As discussed in Chapter 1, older AHAs such as sulfonylureas are more likely to cause adverse effects such as hypoglycaemia than newer AHAs. Improved mechanisms may be required to ensure sufficient communication and collaboration between patients and healthcare workers in remote areas with respect to AHA monitoring and follow-up.

The higher rates of failure of initial sulfonylurea monotherapy, compared to metformin monotherapy, may reflect discontinuation due to more severe adverse events in sulfonylurea users. Sulfonylureas do lower HbA_{1C} more potently than metformin, and part of the reason for their higher failure rate may relate to sulfonylurea initiators having HbA_{1C} levels more substantially above target than

metformin initiators. Nevertheless, this study has brought into question whether sulfonylureas are an appropriate alternative first-line treatment when metformin is contraindicated.

The findings from Chapter 4 were encouraging as they demonstrated that age and frailty are both independently predictive of less intensive AHA therapy being prescribed for older people with T2D and related complications. It also clearly indicated that during the four years following 2012, there was a significant decrease in intensive AHA therapy prescribing in this population. Future research could focus on whether similar trends occur in other settings where older people are at a high risk of experiencing adverse effects from T2D overtreatment, for example in Aged Care Facilities. Promotion of deprescribing of higher risk AHAs such as short-acting or mixed insulins may be needed in hospital settings. For instance, older people with T2D who were hospitalised with hypoglycaemia were over 4 times as likely to receive insulin therapy and over 3 times as likely to receive insulin plus another AHA, compared to those not hospitalised with hypoglycaemia.

Finally, the findings of Chapter 5 indicate that SGLT-2Is are similarly effective in frail versus non-frail people in terms of preventing MACE, compared to DPP-4Is. We also found that SGLT-2Is are no less effective than DPP-4Is in frail versus non-frail people in terms of HHF and all-cause mortality. These findings support the notion that SGLT-2Is may be effective in reducing MACE and HHF regardless of frailty status. Despite this, further studies into other purported adverse events, such as acute renal failure would need to be conducted before definitive recommendations can be made.

6.5 Conclusion

The results generated from this thesis provide important insights into AHA prescribing patterns and clinical outcomes in Australia. Clinical practice guidelines are largely well observed with respect to initial T2D therapy, with metformin or sulfonylurea monotherapy being prescribed for the majority of people initiating AHAs. A minority of people were initially prescribed a non-guideline recommended monotherapy or combination therapy, with the latter more likely to occur in people with fewer comorbidities.

It was also determined that people receive either an addition or a switch of initial therapy more rapidly if they initiate on a sulfonylurea, rather than metformin monotherapy. Longer time periods (up to 2 years) between T2D diagnosis and initiation of the first AHA predicted longer durations before addition of another AHA.

Analysis of AHA prescribing for older patients with T2D and related comorbidities within Melbourne's EH hospital network indicates that older age and increasing frailty reduce the likelihood that clinicians will prescribe various treatment types. Combination prescribing of insulin with other AHAs was significantly less likely in people with high versus low levels of frailty. Over the course of the study (2012 to 2016), AHAs were increasingly less likely to be prescribed across all identified AHA categories. Conversely, older patients hospitalised with hypoglycaemia were more likely to be discharged with a therapy containing insulin, indicating scope for increasing rates of AHA deintensification in this group.

Finally, a large study of all hospitals in the Australian state of Victoria found evidence that frailty did not modify the protective effect of SGLT-2Is on MACE, when compared to DPP-2Is. Furthermore, SGLT-2Is were non-inferior to DPP-4Is in terms of HHF and all-cause mortality. Therefore, this study indicates that SGLT-2Is have cardiovascular benefits in frail individuals which have not previously been recognised and that they may be a suitable alternative to DPP-4Is in this vulnerable sub-population of people with T2D.

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