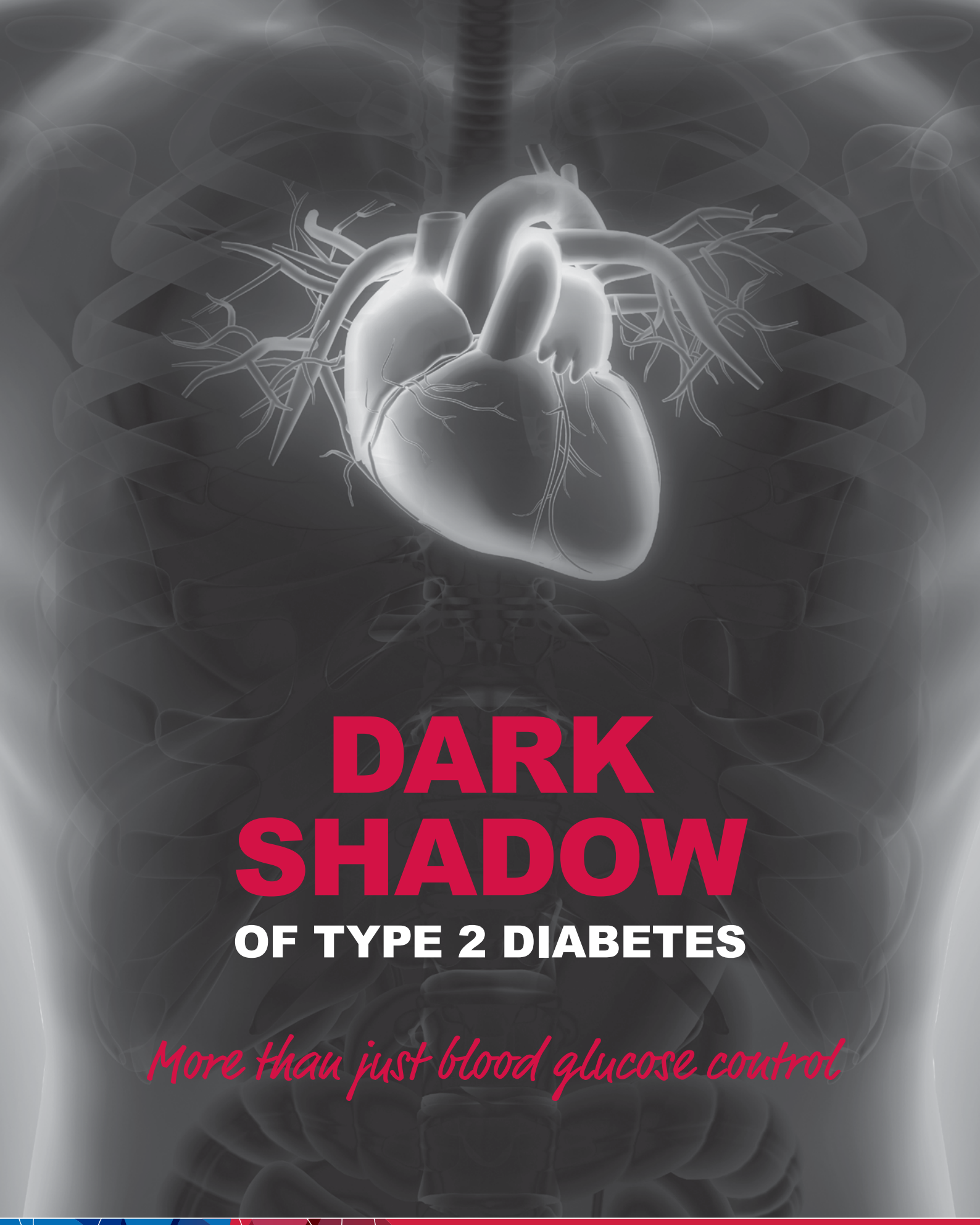

DARK SHADOW

OF TYPE 2 DIABETES

More than just blood glucose control

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Contents

Introduction

Diabetes remains one of the greatest contemporary health challenges. The numbers of people with diabetes are measured in the hundreds of millions globally, and the list of organ systems adversely affected by diabetes continues to grow.

In 2017, we released *The Dark Heart of Type 2 Diabetes* report. This report summarized what was known about the various effects of diabetes on the heart, and provided an estimate of how many lives could be saved if the new class of sodium–glucose co-transporter-2 (SGLT2) inhibitor drugs was used more widely. The report sought to highlight aspects of the effects of diabetes that are not always well-recognised and thereby to increase awareness and improve outcomes for people with type 2 diabetes.

The success of *Dark Heart* in raising these issues prompted us to use a similar format to expand into some of the other complications of diabetes. In this *Dark Shadow* report, we provide up to date information on the impact of diabetes on a broader range of complications. In chapters 1 and 2, we bring the latest information on the major microvascular and macrovascular complications, and, in chapter 3, delve into a number of the other 'non-traditional' complications, including cancer, dementia and liver disease. Wherever possible, we provide information directly relevant to Australia.

Similar to *Dark Heart*, we also look at opportunities to improve outcomes. The last few years has seen a flurry of publications of major trials showing benefits of novel glucose-lowering drugs on both cardiovascular and renal outcomes. Importantly, these benefits did not result from lowering blood glucose, but arose from other, as yet inadequately understood, mechanisms. In chapter 4, we summarize the published literature on the benefits of these agents. Finally, in chapter 5, we estimate the potential population-wide benefits of increasing the uptake of these agents among those at highest risk.

However, not everything is about the latest discoveries. As has been documented repeatedly in many areas of health, there is underuse of interventions whose benefits have already been established over many years. This implementation gap remains wide in type 2 diabetes, and so chapter 5 also provides estimates for how many cardiovascular and renal events could be prevented if there was better use of statins, ACE inhibitors and angiotensin receptor blockers.

Chapter 1

Macrovascular complications of type 2 diabetes

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in adults with type 2 diabetes (1) (Table 1). Compared to their non-diabetic counterparts, those with type 2 diabetes are at approximately two fold increased risk of many manifestations of CVD, including myocardial infarction, heart failure, stroke, peripheral arterial disease and sudden cardiac death. Almost two thirds of people with type 2 diabetes self-report having hypertension or other manifestations of CVD (2) (Figure 1). In one Australian study, one third of people with type 2 diabetes visiting their GP had previously had a heart attack, stroke or had peripheral vascular disease (3). The economic burden of CVD combined with type 2 diabetes at both the patient and population level is significant. Treating CVD costs 20-49% of the total direct cost of diabetes at the population level. Among people with type 2 diabetes, the median annual costs per person with CVD, coronary artery disease, heart failure and stroke are 112%, 107%, 59%, and 322% higher respectively, compared to people with type 2 diabetes but without CVD (4).

Myocardial infarction

In a systematic review including data from 4.5 million people with type 2 diabetes, 10% of the total population had previously had a myocardial infarction (5). In a study of 1.9 million people from the UK of whom 1.8% had type 2 diabetes, diabetes was associated with a 54% increased risk of non-fatal myocardial infarction (6). However, studies from the UK (7) and the USA (8) have shown that the rate of myocardial infarction has declined by approximately a quarter between 1992 and 2012. Studies from Australia have also shown that mortality from CVD among people with type 2 diabetes has been falling (9), although these improvements have not been so clear in younger adults.

Stroke

In the same systematic review as above, 7.6% of the diabetes population had previously had a stroke (5). The risk of stroke appears greater in women than in men, independent of differences in other cardiovascular risk factors (10).

Figure 1. The prevalence of self-reported CVD in people with diabetes (2).

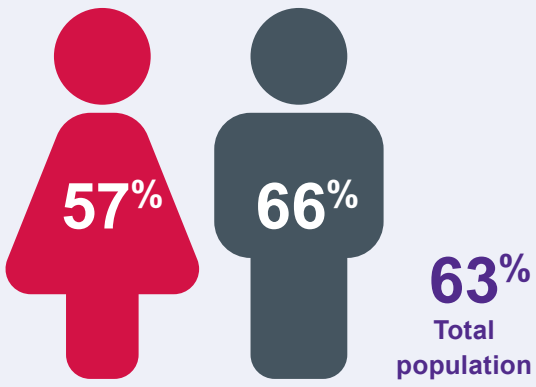


Table 1. The increased risk of cardiovascular disease in people with type 2 diabetes is thought to reflect changes in cardiovascular pathology including:

- Greater plaque burden
- Great complexity of lesions
- Greater coronary calcification
- Greater extent of coronary ischemia
- More multi-vessel disease
- More significantly affected vessels
- Fewer normal vessels
- Reduced coronary collateral recruitment
- Reduced coronary vasodilatory reserve

Cardiovascular deaths

Adults with type 2 diabetes have a two to four fold increased risk of cardiovascular related death compared to those without diabetes (11). Living with type 2 diabetes shortens life expectancy, with the impact being greater with earlier onset diabetes. On average, a 45 year old person with diabetes can expect to live 6 years less than a person free of diabetes, with many of these earlier deaths being due to CVD (12). In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, a population based study including 11,247 adults aged 25 years and older, across Australia, approximately 34% of all deaths were attributable to CVD across a 5-year period (13) – two thirds of these deaths occurred in people who had either type 2 diabetes or prediabetes. Nevertheless, there is evidence of some improvement. Data in over 1 million Australian adults with diabetes on our National Diabetes registry, showed that the cardiovascular death rate fell from 2002-2011 in both men and women (9). Unfortunately, the declines in mortality were not consistent across all ages, with people at younger ages (0-40 years) experiencing lesser declines than older adults.

Indigenous Australians are nearly four times more likely to have type 2 diabetes compared to non-Indigenous Australians (14). In 2013–14, hospitalisations in which type 2 diabetes was the principal or additional diagnosis were four times more frequent in Indigenous Australians compared to non-Indigenous Australians. Rates of hospitalisation of Indigenous people for diabetes increased with age. However the greatest gap between Indigenous and non-Indigenous Australians occurs at younger ages. Between the ages of 25 and 44 years, hospitalisation rates were 14 times higher in Indigenous than non-Indigenous Australians (14). Ischemic heart disease is the leading cause of death in Indigenous Australians with a population rate 1.8 times higher than that of non-Indigenous Australians (15). The excess relative risk is even greater in people of younger ages, with 12% of deaths in Indigenous Australians aged 30-39 years being attributable to CVD compared to 4% in non-Indigenous Australians.

Figure 2. Percentage of deaths attributable to CVD in Indigenous Australians aged 30-39 years compared to non-Indigenous Australians of the same age (15).

Heart failure

Heart failure is a complex syndrome characterized by symptoms easily confused with diabetes itself or other co-morbidities such as obesity (i.e. dyspnea and fatigue, Table 2). Type 2 diabetes and heart failure often occur in conjunction with each other, as each disease independently increases the risk of the other. Heart failure has been reported in 12-57% of those with type 2 diabetes (16) and occurs up to 8 times more frequently in people with diabetes, compared to those without.

Heart failure has typically been viewed as the final stage of structural heart disease, most commonly resulting from previous infarction or from valvular disease. However, it has become increasingly recognized that heart failure can be the very first presentation of heart disease, and may occur in the absence of either coronary artery or valvular heart disease, especially among people with diabetes. Indeed, in a study of nearly two million people in the UK, heart failure was the second most common initial manifestation of CVD (after peripheral arterial disease) in people with type 2 diabetes (6). Thus, in many people, heart failure was not preceded by coronary artery disease, and can arise directly from the metabolic effects of diabetes on the myocardium.

Heart failure is emerging as a leading cause of death in type 2 diabetes (17), the 5-year survival rate being worse than that of many cancers. Studies have also demonstrated that even mild elevations in blood glucose levels or abnormalities in insulin sensitivity are associated with increased risk of heart failure (18, 19). Furthermore, the Framingham Heart Study showed in 5881 participants, that the increased risk of heart failure per one unit increase in body mass index was 5% in men and 7% in women, even after adjusting for demographics and known risk factors (20). The continuous relationship between higher body mass index and risk of heart failure has also been shown in other large studies (21, 22).

Among people with heart failure, type 2 diabetes is associated with reduced quality of life, more hospital admissions, longer admissions and more readmissions. An

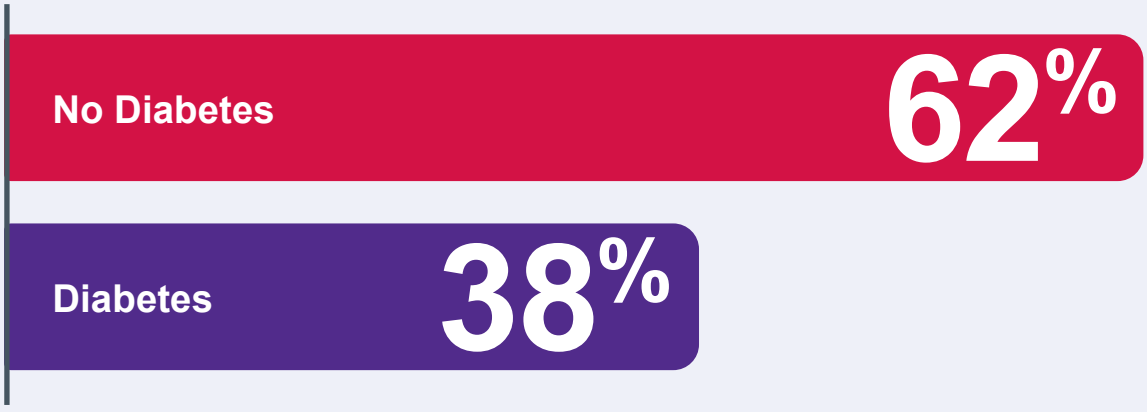
Table 2. Common signs and symptoms of heart failure.

Australian study showed that more than a third of acute admissions for heart failure were in people with type 2 diabetes (23) (Figure 3). In a study of Australian Veterans, nearly one in four older patients hospitalised for diabetes, were re-admitted within 30 days, with heart failure being one of the strongest predictive factors of readmission (24). Importantly, the average cost per hospitalisation for any admission in Australia for people with type 2 diabetes is $8755 (25), thereby posing a significant economic burden.

Practice Point

Think of heart failure as a potential cause of breathlessness or exercise intolerance, even when there has been no prior cardiac disease.

Figure 3. The percentage of admissions with acute heart failure in which diabetes was or was not present (23)



Chapter 2

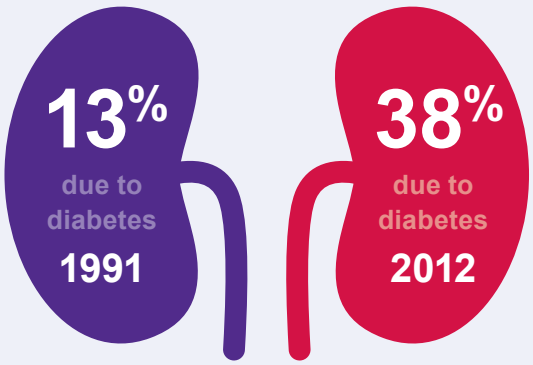
Microvascular complications of type 2 diabetes

Kidney disease

People with type 2 diabetes are nearly two times more likely to have chronic kidney disease (CKD) compared to those without diabetes. Data from an Australian study (AusDiab) found that among adults aged 25 years and older with type 2 diabetes, 27% had evidence of CKD. These data suggest that a quarter of a million Australians have CKD and are at risk of end stage renal disease, cardiovascular events and premature death. By comparison in the US, the prevalence of CKD in type 2 diabetes is 44% in the overall population (mean age 64 years) according to results from the NHANES 1999–2012 data (26).

Diabetes is the most common cause of end-stage kidney disease (ESKD, i.e. dialysis or kidney transplant). For example, in Australia, diabetes is the primary cause of 37% of all cases of ESKD (27). In most other countries around the world, diabetes is also the most common cause of ESKD, with a number of Asian countries reporting that diabetes accounts for 40-50% of all ESKD. Among Indigenous Australians, the burden of ESKD is even greater. The overall risk is four times greater than among non-Indigenous Australians, and 70% is due to diabetes (28).

Figure 4. Percentage of new end stage kidney disease cases with a primary diagnosis of diabetes in 1991 and 2012.



Practice Point

Aggressive risk factor management is vital in younger adults with type 2 diabetes to reduce the very high risk of complications.

Compared to those without type 2 diabetes, the incidence of ESKD is as much as 10 times higher in those with diabetes. In Australia in 1991, 13% of new ESKD cases had a primary diagnosis of diabetes, compared to 38% in 2012 (29) (Figure 4). The growth in ESKD is predominantly due to increased prevalence of type 2 diabetes, improved survival in this population and greater willingness to treat sicker and older patients with ESKD (30). Recent national Australian data from the Australian and New Zealand Dialysis and Transplant Registry showed that while the incidence of ESKD was slowly falling in those with type 2 diabetes aged 50-80, it was rising in those aged under 50 years (31). It is possible that this rise is being driven by the younger age of onset of type 2 diabetes, and perhaps less aggressive risk factor management in younger adults with type 2 diabetes. This study also confirmed the much higher incidence of ESKD in the Indigenous population.

Amputations

Lower extremity amputations are a major complication of type 2 diabetes, as they pose a significant physical, economic and psychosocial burden. Indeed, diabetes is responsible for the majority of non-traumatic lower-limb amputations. There were 4,402 lower-limb amputations in people with diabetes in Australia between 2012-13 (32). They typically result from foot ulceration, which, in turn, is usually due to peripheral arterial disease, peripheral neuropathy, or a combination of the two.

Lower-limb amputations are more common in males (75% of all lower-limb amputations) and in those aged 65 years and over (58% of all lower-limb amputations) (32). However, there have been reductions in lower extremity amputations since 1982 worldwide. In Australia, lower extremity amputations rates fell by 2.4% per year between 2000 and 2010, driven primarily by a decline in major amputations (i.e. those above the foot) (33). Globally, the decline in amputations appears to have been driven by a reduction in major amputations, with smaller declines, and in some cases increases, in minor amputations (34). Regular screening for neuropathy and peripheral arterial disease, aggressive management of early foot problems and the ready availability of multi-disciplinary foot clinics have been the reason for these improvements in amputation rates. It is noteworthy that even within a single health service in England, rates of amputation varied 5-10-fold across geographic districts, with variation in care likely to account for much of this (35).

In people with diabetes, those of Indigenous descent are at an increased risk for amputation. Among those with diabetes aged 25-49 years, Indigenous people are 27 times more likely to have a minor amputation (toe or foot) and 38 times more likely to have a major amputation (above the knee) compared to non-Indigenous people (36). Furthermore, nearly all (98%) non-traumatic amputations in Indigenous people are related to diabetes.

Eye disease

Diabetic eye disease is a leading cause of irreversible vision loss and blindness in working age adults worldwide. A study involving 33 countries globally found that approximately one third of people with type 2 diabetes have diabetic retinopathy and one in 20 have diabetic macular oedema (37). Diabetic retinopathy is the main cause of vision loss in non-Indigenous and Indigenous Australian adults with known diabetes. The National Eye Health Survey (NEHS) showed that the prevalence of any diabetic retinopathy in Australia is 29% among non-Indigenous adults with diabetes and 44% among Indigenous adults with diabetes (38) (Figure 5). The NEHS also showed that the prevalence of macular oedema is higher in Indigenous Australians compared to non-Indigenous Australians (15% vs 6%) (38). The expected increase in the number of those people living with type 2 diabetes in Australia in the coming decades will lead to an increased number of people with diabetic eye disease or vison loss.

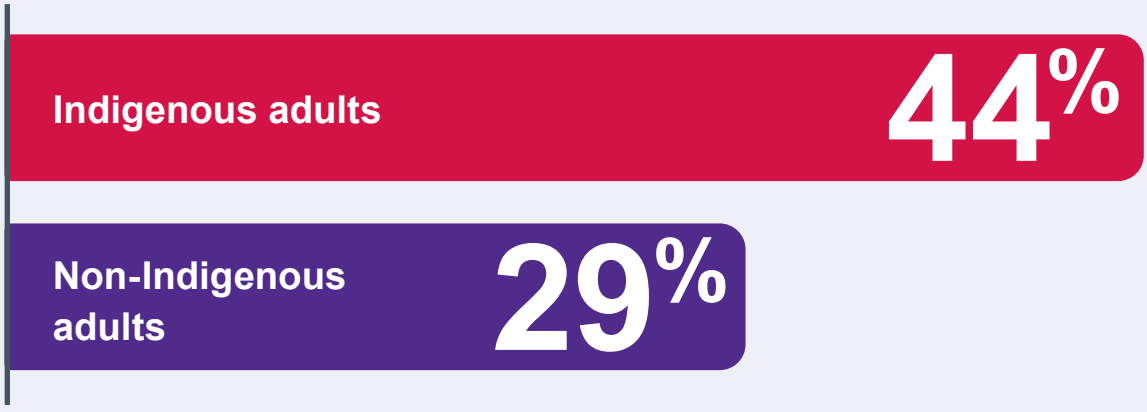
People with diabetes are also at a higher risk of developing other eye conditions such as cataracts, which in most cases requires treatment to reverse vision loss. A meta-analysis involving approximately 20,000 people, showed that adults with type 2 diabetes are almost twice as likely to develop cataracts compared to those without diabetes (39). Data from the Fremantle Diabetes Study showed that adults with type 2 diabetes, especially younger adults, are at a significantly increased risk of cataract surgery (40).

Regular eye checks are essential to identify and monitor the early stages of diabetic eye disease so that risk factors for worsening disease can be managed and treatment can be delivered at the most appropriate time. It is recommended that a diabetic eye check be performed when diabetes is diagnosed and at least every two years thereafter, except in those at higher risk of diabetic retinopathy such as Indigenous Australians or those with a longer duration of diabetes where at least annual eye checks are recommended (41). However, many people with diabetes do not receive eye examinations in a timely fashion. Among Australians with diabetes, studies have reported that 22-50% of people are not meeting guidelines for appropriate frequency of eye examinations (38, 42). This may actually under-estimate the problem, as these data rely on self-report, and some people reporting eye examinations may not have had a full examination of the retina.

Practice Point

Ensure that all people with diabetes are up to date with eye examinations, with a full retinal assessment at least every second year.

Figure 5. Prevalence of any diabetic retinopathy among Indigenous adults with diabetes (red) and non-Indigenous adults with diabetes (purple) (38).



Chapter 3

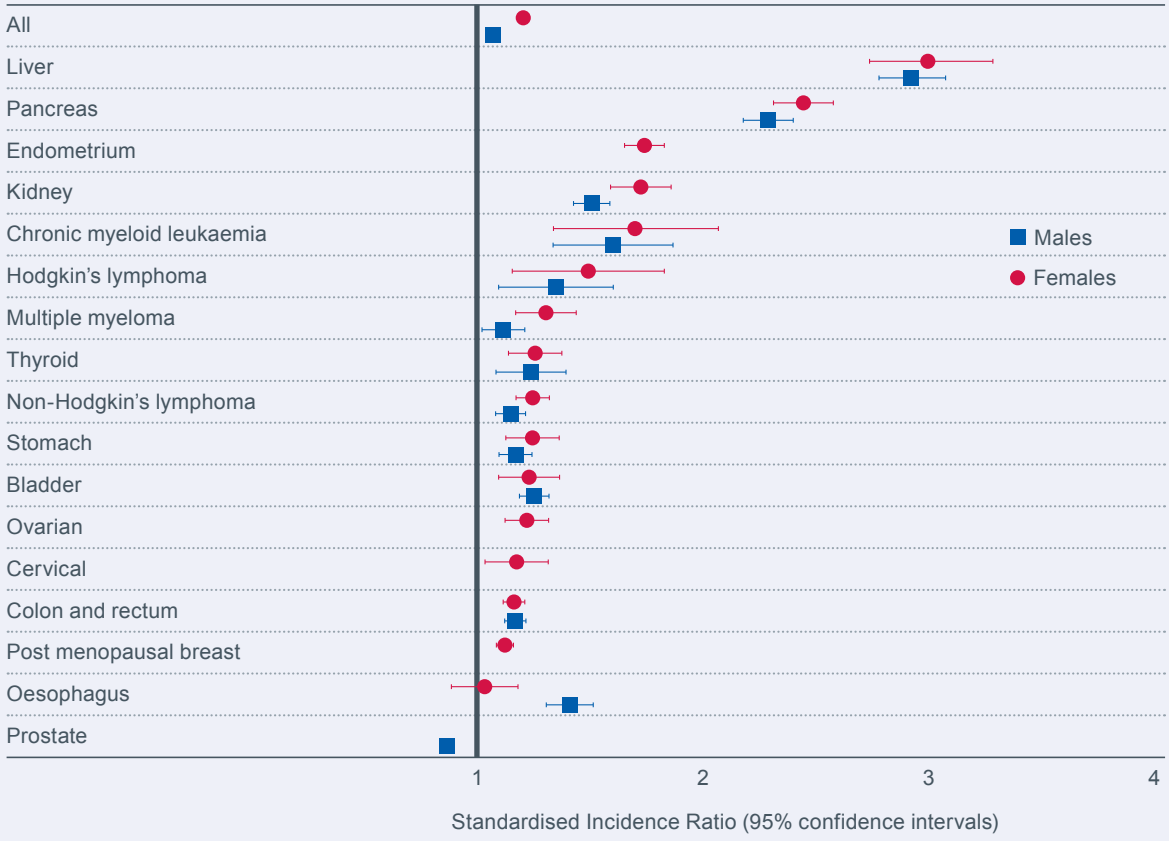
Non-traditional complications

The micro- and macro-vascular complications of diabetes described above have long been recognized as important consequences of diabetes. However, it is increasingly being recognized that diabetes increases the risks of numerous other diseases. As life-expectancy increases, and treatment of the classical diabetes complications improves, these other comorbidities are becoming important co-morbidities of diabetes.

Cancer

An international review showed that people with type 2 diabetes are at an increased risk of developing many types of cancer. This includes a two- to three-fold increase in incidence of pancreatic cancer, two-fold increase in liver cancer, two-fold increase in endometrial cancer, a 30% increase in colorectal cancer and a 20% increase in breast cancer. However, prostate cancer risk is consistently lower in men with type 2 diabetes (43). Similar relationships between diabetes and cancer among Australians are shown in Figure 6 (44). In an Australian study involving 1 million people with diabetes, all-cause and CVD mortality rates decreased between 2000 and 2011, but cancer mortality rates remained unchanged. Importantly, in those aged 0-40 years, a significant increase in cancer mortality over the same period was observed.

Figure 6. The risk of developing cancer in people with diabetes compared to the general population (44).

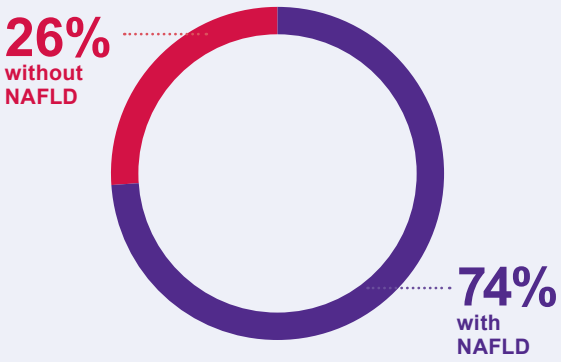


Standardised incidence ratio is a comparison of the incidence in people with diabetes, with the incidence in the age- and sex-matched general population.

Practice Point

Ensure that all people with diabetes keep up to date with all standard cancer screening programs.

Figure 7. Prevalence of NAFLD among people with type 2 diabetes (48).



Dementia

Dementia is a relatively recently recognised complication of type 2 diabetes. A meta-analysis involving data from 2 million people, showed that people with type 2 diabetes have a 60% greater risk of developing dementia compared to those without diabetes (45). Importantly, this increased risk applied not only to vascular dementia, but also to Alzheimer's disease. Furthermore, the effect of diabetes on risk of vascular dementia differed between men and women. The excess risk for vascular dementia attributable to diabetes was 19% greater in women than in men. Another meta-analysis involving 1.7 million people showed that the effect of diabetes on risk of Alzheimer's disease was greater in East Asian populations than in Western populations (62% vs 36% increased risk) (46). The AusDiab study showed that even elevations of fasting glucose within the normal range were associated with a measurable impairment in cognitive function 12 years later (47).

Liver disease

Non-alcoholic fatty liver disease (NAFLD) has been recognised as a common co-morbidity in people with type 2 diabetes. In the US, data from NHANES showed that 74% of those with diabetes had NAFLD (Figure 7), translating to approximately 22.3 million people. However, this figure was stable between 2003 and 2014 (48). Type 2 diabetes, metabolic syndrome and concurrent NAFLD likely contribute to progression of hepatic fibrosis and cirrhosis (49). Indeed, the development of cirrhosis is two-fold higher in people with type 2 diabetes compared to those without diabetes (50, 51). One study showed in a large cohort of those with NAFLD, that the prevalence of diabetes and degree of fibrosis progressed in parallel, suggesting that type 2 diabetes is a risk factor for advanced fibrosis in people with NAFLD (52). Indeed, diabetes (53, 54), insulin resistance (55) and glucose levels (56) are each associated with progression of hepatic fibrosis in patients with chronic liver disease.

A wide range of other diseases and conditions are also more common in diabetes. These include depression, physical frailty, osteoporosis, sleep apnea, hearing impairment, infections, glaucoma, cataracts, and periodontal disease.

Chapter 4

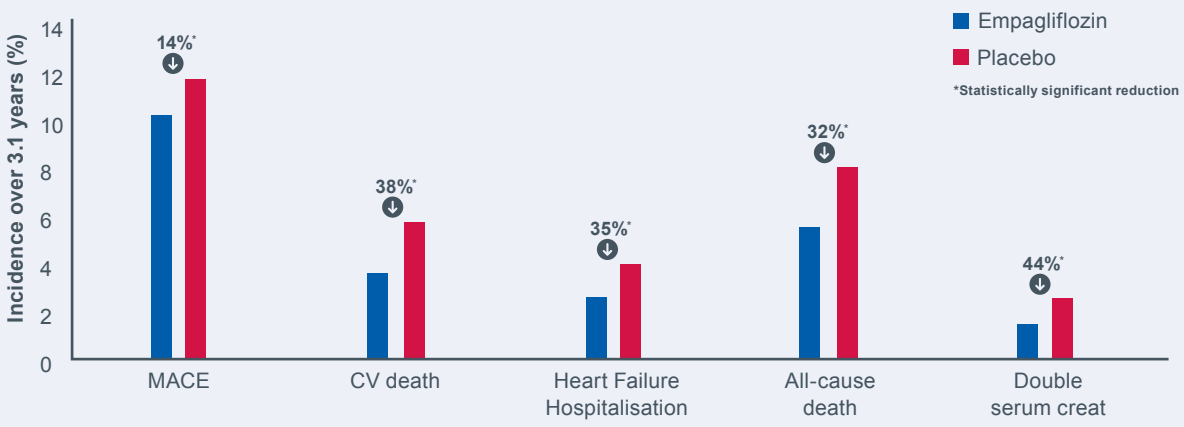
Novel medications for type 2 diabetes

Benefit of novel diabetes drugs beyond glucose lowering effects

Despite the fact that diabetes considerably increases the risk of developing CVD, studies have not shown a clear and consistent benefit of tight blood glucose control for preventing CVD. The UK Prospective Diabetes Study (UKPDS) involving 5102 individuals with newly diagnosed diabetes showed that intensive blood glucose control only improved cardiovascular risk in a small sub-group treated with metformin (57). For those who were treated with insulin or sulphonylureas, statistically significant CVD benefits were only apparent after more than 10 years of follow-up (58). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study, a randomised controlled study in 10,251 people with type 2 diabetes, showed that intensive control of blood glucose increased the risk of death and did not reduce major cardiovascular events after 3.5 years follow up (59). A meta-analysis of five randomised controlled trials (including UKPDS and ACCORD), showed that intensive glucose lowering resulted in a modestly lower event rate for coronary heart disease, but no benefit for stroke or all-cause mortality (60). It should be noted that tight glycaemic control is, nevertheless, very effective for reducing the risk of microvascular disease. Together, these findings indicate that reducing the excess CVD risk in people with diabetes requires far more than just controlling blood glucose levels. Addressing blood pressure and lipid levels are of importance, but recent trials have also shown that new classes of anti-diabetic medications have major cardio- and reno-protective effects, beyond glucose lowering. The efficacy of these medications is summarised in Table 3.

Empagliflozin, an SGLT2 inhibitor, is one of the newer anti-diabetic medications. SGLT2 inhibitors inhibit the reabsorption of glucose in the kidney, resulting in loss of glucose into the urine, and lower blood glucose levels. The effects of empagliflozin on cardiovascular outcomes were assessed in a major trial – the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose (EMPA-REG) study. This trial included 7020 people with type 2 diabetes and prior CVD who were followed for a median of 3.1 years and compared empagliflozin with placebo. The main outcome measure was a composite of

Figure 8. Cardiorenal outcomes in the EMPA-REG trial and percent difference between empagliflozin and placebo (61, 62).



myocardial infarction, stroke and cardiovascular death (collectively called MACE – major adverse cardiovascular events), which was significantly reduced by 14%. In addition, there were major reductions in hospitalisation for heart failure, cardiovascular death, death from any cause and the progression of renal disease (Figure 8) (61, 62).

Similar findings were observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) in 10,142 people with type 2 diabetes at high CVD risk but better renal function compared to the EMPA-REG trial, followed for 3.6 years. Compared to placebo, the canagliflozin group had a significant reduction in MACE, which was reduced by 14%, and in heart failure hospitalisations which were reduced by 33%. However, it should be noted, there was an increased risk of amputation in the canagliflozin group (63), though this has not been seen in any of the other SGLT2 inhibitor trials, and may have been a chance finding. Most recently, similar benefits for heart failure and renal disease were reported in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial (64). However, there was no significant effect of the active treatment on MACE or all-cause mortality compared to placebo. Importantly, the DECLARE population was mainly free of CVD at baseline, indicating that the benefits of SGLT2 inhibitors include both primary and secondary prevention of CVD. Taken together, these three trials show major benefits of SGLT2 inhibitors for heart failure and renal disease with smaller benefits for myocardial infarction and stroke (Table 3).

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, semaglutide and dulaglutide, have also demonstrated cardio-protective effects in people with type 2 diabetes (Table 3). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results-A Long Term Evaluation (LEADER) trial, which involved 9340 people with type 2 diabetes at high risk of CVD or with existing CVD, followed for a median time of 3.8 years, showed that liraglutide compared to placebo resulted in a 13% statistically significant reduction in MACE, as well as a 15% reduction in death from any cause. The Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) study enrolled 3297 people with type 2 diabetes and CVD or at high risk, and demonstrated a 26% reduction in MACE compared to placebo. In a trial of nearly 10,000 people with diabetes, most of whom did not have established CVD, and had adequate glycaemic control, dulaglutide led to a 12% reduction in MACE (65). Other GLP-1 receptor agonists (lixisenatide and exenatide) did not demonstrate superiority over placebo in terms of cardiovascular outcomes.

It should be noted that by design the two study arms of each of these trials had similar HbA1c levels, as doctors were allowed to use a wide range of other drugs to achieve appropriate HbA1c targets. This suggests that these newer anti-diabetic medications demonstrate cardio-protective effects through mechanisms which are independent of glucose lowering. The benefits of these two medication classes are most clearly demonstrated among those with established CVD, and the combination of type 2 diabetes and a previous cardiovascular event should now routinely prompt the consideration of adding a drug from one of these classes. In addition to the benefits in such high-risk individuals, at least two of the trials (64, 65) extend these findings to lower risk people who did not have established CVD. Observational, ‘real-world’ analyses also support the conclusion that benefits extend to a much broader and lower risk population (66, 67).

Safety considerations

There are some safety issues related to use of these novel diabetes drugs that should be considered. SGLT2 inhibitors have been associated with an increased risk of fungal genital infections, and volume depletion and canagliflozin was also associated with increased risk of amputation of the toes, feet or legs and fracture (62, 63). Additionally, use of SGLT2 inhibitors has been associated with a rare side effect of euglycemic diabetic ketoacidosis (68). Side effects of GLP-1 receptor agonists include nausea and vomiting.

Practice Point

All people with type 2 diabetes and established CVD should be considered for treatment with an SGLT2 inhibitor or GLP-1 receptor agonist, even if blood glucose control appears adequate.

Table 3. Effects of SGLT2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes

	Reduction in outcome			
Drug	**Non-fatal MI/ non-fatal stroke/ CVD death**	**Heart Failure hospilisation**	**All-cause mortality**	**Renal disease[c]**
SGLT2 inhibitors				
Empagliflozin (61, 62)	14%	35%	32%	46%
^Canagliflozin (63)	14%	33%	13% (NS)	40%
Dapagliflozin (64)	7% (NS)	27%	7% (NS)	24%
GLP-1 receptor agonists				
Liraglutide (69)	13%	13% (NS)	15%	12%
Semaglutide (70)	26%	11% increased risk (NS)	5% increased risk (NS)	36%
Dulaglutide (65)	12%	7% (NS)	10% (NS)	15%
^Lixisenatide (71)	2% increased risk (NS)[a]	4% (NS)	6% (NS)	
Exenatide (72)	9% (NS)	6% (NS)	14%	12% (NS)
^Albiglutide (73)	22%	15% (NS)[b]	5% (NS)	

[a] Outcome was cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina.
[b] Composite of cardiovascular death and heart failure hospitalisation
[c] Renal outcomes varied among trials. All were composite outcomes that included a significant reduction in eGFR, with or without end stage renal disease and microalbuminuria.

MI, myocardial infarction; CVD, cardiovascular disease; NS, non-significant.

Chapter 5

Opportunities for improvement

Substantial evidence now exists for the benefit of interventions that will reduce the risks of developing cardiovascular and renal outcomes in people with diabetes. In addition to the studies described in chapter 4 showing the effects of SGLT2 inhibitors and GLP-1 agonists, many earlier studies have demonstrated the cardio-protective effects of ACE inhibitors, angiotensin receptor blockers (ARB), other anti-hypertensive drugs, statins and anti-platelet therapy. Guidelines have, for a number of years, recommended that these agents are used routinely in those with established CVD, and used widely in those people with increased risk based on the presence of risk factors.

Despite these well-established recommendations, studies repeatedly show that many people who are at risk, and would benefit from more intensive cardio-protective therapy, are not receiving it, and are failing to achieve the recommended treatment targets. One study of patients attending specialist clinics found that only about 55-65% of patients at two Australian diabetes clinics were prescribed an ACE inhibitor or an ARB, with 60-70% being prescribed a statin (74). A study of over 70,000 patients with diabetes from the US showed that only one in four met all three of the HbA1c, LDL-cholesterol and blood pressure targets (75). Australian data showed that 43% of people who initiated statin therapy discontinued within 6 months (76).

Thus, there is a significant evidence-practice gap.

In order to quantify the potential gains that might be achieved by reducing this gap, we present, here, estimates of the numbers of cardiovascular and renal events that could be prevented or delayed, within the population of Australians with type 2 diabetes, if the uptake of drugs known to have cardiovascular and renal benefits was increased.

In undertaking this, we have used only the highest level of data, from large randomized controlled trials and meta-analyses, in which the effect of each type of intervention on hard clinical outcomes has been shown to be statistically significant. Therefore, we have modelled the effects of increasing the use of SGLT2 inhibitors, GLP-1 receptor agonists, statins, and renin-angiotensin system blockade (i.e. ACE inhibitors and ARBs). Based on information about current usage of these drugs in the Australian population with type 2 diabetes, we have modelled the effects of increasing that use by potentially achievable amounts. Thus, we modelled larger increases in uptake of SGLT2 inhibitors and GLP-1 receptor agonists, as they have fairly limited use currently, and smaller increases in well-established drugs such as statins and ACE inhibitors.

The findings should be seen as estimates of the general size of the potential benefits to the Australian population of increasing the use of these therapies. It should be noted that no medications are free of side effects, and that no estimates are provided here of the potential increase in adverse events. However, each of the drugs modelled here has shown benefits for either all-cause mortality or for major clinical cardiovascular or renal outcomes. Therefore, it can be assumed that, when used in high-risk populations, there is a net benefit. The aim of this analysis was to estimate the population-level effects of increasing the use of specific classes of medications on cardiovascular disease and kidney events in Australian adults with type 2 diabetes.

Methods

The numbers of people with type 2 diabetes, as well as the number who are already on the relevant medications were estimated from the National Diabetes Service Scheme (NDSS) database and Pharmaceutical Benefit Scheme (PBS) database. We used clinical trial results to quantify the benefit of each class of medication on specific cardiovascular and kidney disease outcomes. These outcomes include major adverse cardiovascular events (MACE, i.e. non-fatal stroke, non-fatal heart attack, and deaths caused by cardiovascular disease), death caused by cardiovascular disease, end-stage kidney disease (ESKD - dialysis or kidney transplant), and hospitalisation for heart failure (HHF). By applying the quantified benefit of these medications to the incidence rate of the outcomes, we were able to estimate how many disease events could be prevented in a single year if the usage of each drug was increased. That is, how many MACE events, HHF events, ESKD events and deaths caused by cardiovascular disease could have been prevented.

The best established effects of SGLT2 inhibitors and GLP-1 agonists are among those people with established CVD, and so analyses for these drug classes were restricted to this population. The effects of statins, ACE inhibitors and ARBs are robustly established in the broader population, which is, therefore, used for analyses of the effects of these drug classes. Furthermore, since different trials have reported different outcomes, the outcomes that are presented here differ in line with the trial data.

More detailed methods are provided in the appendix.

Results

There were 963,066 Australians with type 2 diabetes on the NDSS in 2015, among whom 227,624 were aged 40-79, and were estimated to have prior CVD. Within this group, there were 6,473 MACE, 2,200 HHF and 236 ESKD events in the year 2015. Among those on the NDSS aged 40-79, irrespective of prior CVD or treatment, there were 4,239 CVD deaths in 2015.
In the analysis modelling glucose-lowering medications, we found that assuming that half of the eligible population take the drugs, the introduction of SGLT2 inhibitors would reduce the number of people having MACE events in a single year by 453, while GLP-1 agonists reduced the number of MACE events by 421 (Table 4). As the uptake of SGLT2 inhibitors and GLP-1 agonists increases to 75%, the number of MACE prevented increased to 680 and 631 respectively. The number of HHF and ESKD events which were prevented using SGLT2 inhibitors, at 50% or 75% usage, are shown in Table 4. For statins and antihypertensive medications, the number of CVD deaths which could be prevented, assuming the population taking these increased by 20%, were 162 and 143, respectively (Table 5).

Table 4. Number of events prevented in one year across Australia according to the percentage of those aged 40-79 with type 2 diabetes and prior CVD who use SGLT2 inhibitors and GLP-1 agonists.

a)

Type of medication	MACE events prevented	
	50% usage	75% usage
SGLT2 inhibitors	453	680
GLP-1 agonists	421	631

b)

Type of medication	Hospitalisation for heart failure episodes prevented	
	50% usage	75% usage
SGLT2 inhibitors	341	511

c)

Type of medication	ESKD events prevented	
	50% usage	75% usage
SGLT2 inhibitors	52	78

Table 5. Number of events prevented in one year across Australia resulting from a 20 percentage point increase in use of statins and ACE inhibitors or ARBs in those aged 40-79 with type 2 diabetes.

Type of medication	CVD deaths prevented
Cholesterol lowering medications	162
ACE inhibitors or ARBs	143

Discussion

These findings indicate the likely magnitude of effects of the widespread introduction of SGLT2 inhibitors, GLP-1 agonists, and increase in use of statins, ACE inhibitors and ARBs on various outcomes among those with type 2 diabetes. If the effects of SGLT2 inhibitors reported in trials were reproduced in the general diabetes population, and 50% of people with diabetes and prior CVD were prescribed SGLT2 inhibitors, then over 800 MACE, ESKD and HHF events could be prevented in a single year. Prescribing the same population with GLP-1 agonists, would prevent over 400 MACE events. Greater benefits would be seen if usage were to reach 75% of those with prior CVD. If the numbers of those with diabetes taking statins, ACE inhibitors and ARBs increased, an additional 162 or 143 deaths could be prevented, respectively.

This information adds to what is known from clinical trials by providing a meaningful impact across the Australian population. The effects described here in a single year would clearly be significantly magnified over time, and show the potential benefits of working towards ensuring that as many people as possible with type 2 diabetes and at high cardiovascular risk are taking evidence-based medications. Furthermore, in regard to the SGLT2 inhibitors and GLP-1 agonists, only their benefits in those with established CVD were considered, since there are now several trials consistently showing benefits in this group. However, there is accumulating evidence that some of the benefits are also seen in people with type 2 diabetes and multiple CVD risk factors, even in the absence of established CVD. Thus, the potential for reducing morbidity and mortality is likely greater than estimated here.

It is important to consider the limitations of the results presented here. The findings presented do not take into account any the adverse events of these medications. Further, this analysis does not examine the costs of medications. In order to obtain the maximum benefit reported here, about 110,000 people would need to take SGLT2 inhibitors, and remain on the drug throughout the one-year time-period that was considered. However, for many people, SGLT2 inhibitors, or GLP-1 agonists would be used instead of another drug in order to achieve adequate glycaemic control. Thus, in considering costs, the difference between drug costs, rather than simply the absolute cost of SGLT2 inhibitors, or GLP-1 agonists, needs to be assessed.

In summary, we have shown that, within the Australian type 2 diabetes population, there are significant opportunities to reduce the population-wide burden of cardiovascular and renal outcomes by increasing the use of novel and of well-established drugs.

Appendix

Detailed methods for chapter 5

The aim of this analysis was to estimate the population-level effects of increasing the use of specific classes of medications for the prevention of cardiovascular and kidney outcomes in people with type 2 diabetes. These medications include glucose-lowering drugs, cholesterol-lowering agents, and anti-hypertensive medications. The outcomes we were interested in were major adverse cardiovascular events (MACE, i.e. non-fatal stroke, non-fatal heart attack, and deaths caused by cardiovascular disease (CVD)), CVD mortality, end stage kidney disease (ESKD), and hospitalisation for heart failure. The source of the national diabetes population was the National Diabetes Service Scheme (NDSS). The NDSS was linked to the National Death Index (NDI) using data up to and including April 2016. All-cause and CVD mortality rates among those with type 2 diabetes were estimated by Poisson regression using this population. We used the 2015 NDSS population. The NDSS does not include information on the presence of CVD. We therefore used data from the national, population-based Australian Diabetes Obesity and Lifestyle Study (AusDiab) to calculate the prevalence of CVD among adults with type 2 diabetes. We used data from the Fremantle Diabetes Study to estimate the relative risk of CVD mortality associated with prior CVD among people with diabetes. We then applied these (in an age-specific manner) to the NDSS population and NDSS CVD mortality data, using standard methods of apportioning a rate into two groups using prevalence and relative risks. This method apportions the CVD mortality rates for the total NDSS diabetic population into those with prior CVD and those without. The relative risks were then combined with CVD mortality rates for the year 2015 for the NDSS population, and with age-specific prevalence of prior CVD in diabetes, to calculate the CVD mortality rate for the population without prior CVD among diabetes and the CVD mortality rate for the population with prior CVD among diabetes.

We performed these calculations in four age groups: 40-49, 50-59, 60-69 and 70-79 years. Where possible, we sourced incidence rate of non fatal outcomes from Australian data. Incidence rates of ESKD were obtained from the NDSS data linked to Australian and New Zealand Dialyses and Transplant register. As the incidence of MACE in Australia is not easily obtained, we estimated this rate by applying a ratio of MACE events to CVD mortality (from a meta-analyses of diabetes outcome trials) to CVD mortality rates derived from NDSS, estimated as above. Similar estimations were made to derive a hospitalisation for heart failure rate.

We modelled various medications with different scenarios and several hard outcomes. For glucose lowering drugs, we estimated the potential benefit of 50% and 75% of everyone with type 2 diabetes with prior CVD events taking these medications. For cholesterol-lowering and anti-hypertensive medications, we estimated the potential benefit if the number of people with type 2 diabetes (irrespective of their CV history) who are taking these medications was increased by 20 percentage points. The efficacies of these medications on the specified outcomes were obtained from clinical trial results. We only modelled the effect of medication on outcomes where there was significant benefit from trials. We quantified the benefit of each medication by applying the relative risk reduction from published RCTs to the incidence rate of the MACE, ESKD and hospitalisation for heart failure for SGLT2 inhibitors, and on the incidence of MACE for GLP-1 agonist use. That is, we estimated how many MACE events, ESKD events or hospitalisations for heart failure could have been prevented if 50% and 75% of eligible individuals were taking the medications. For lipid lowering medications and antihypertensive medications, we modelled the effect of the medications on CVD mortality only among those with type 2 diabetes assuming we could increase the usage of these agents by 20 percentage points.

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Baker Heart and Diabetes Institute

The Baker Heart and Diabetes Institute is an independent medical research institute with a mission to reduce death and disability from cardiovascular disease, diabetes and related disorders. The Baker Institute is one of the few institutes in the world where the work of world-leading clinicians and researchers spans the spectrum of chronic disease from obesity to type 2 diabetes and cardiovascular disease, and ranges from benchtop to bedside to population.

The Institute is acutely aware of the need to meet the significant challenges facing the community as a result of rising rates of diabetes and cardiovascular disease. In particular, the Institute is committed to raising awareness of the important relationship between type 2 diabetes and cardiovascular disease to help improve the quality of life for patients with type 2 diabetes.

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