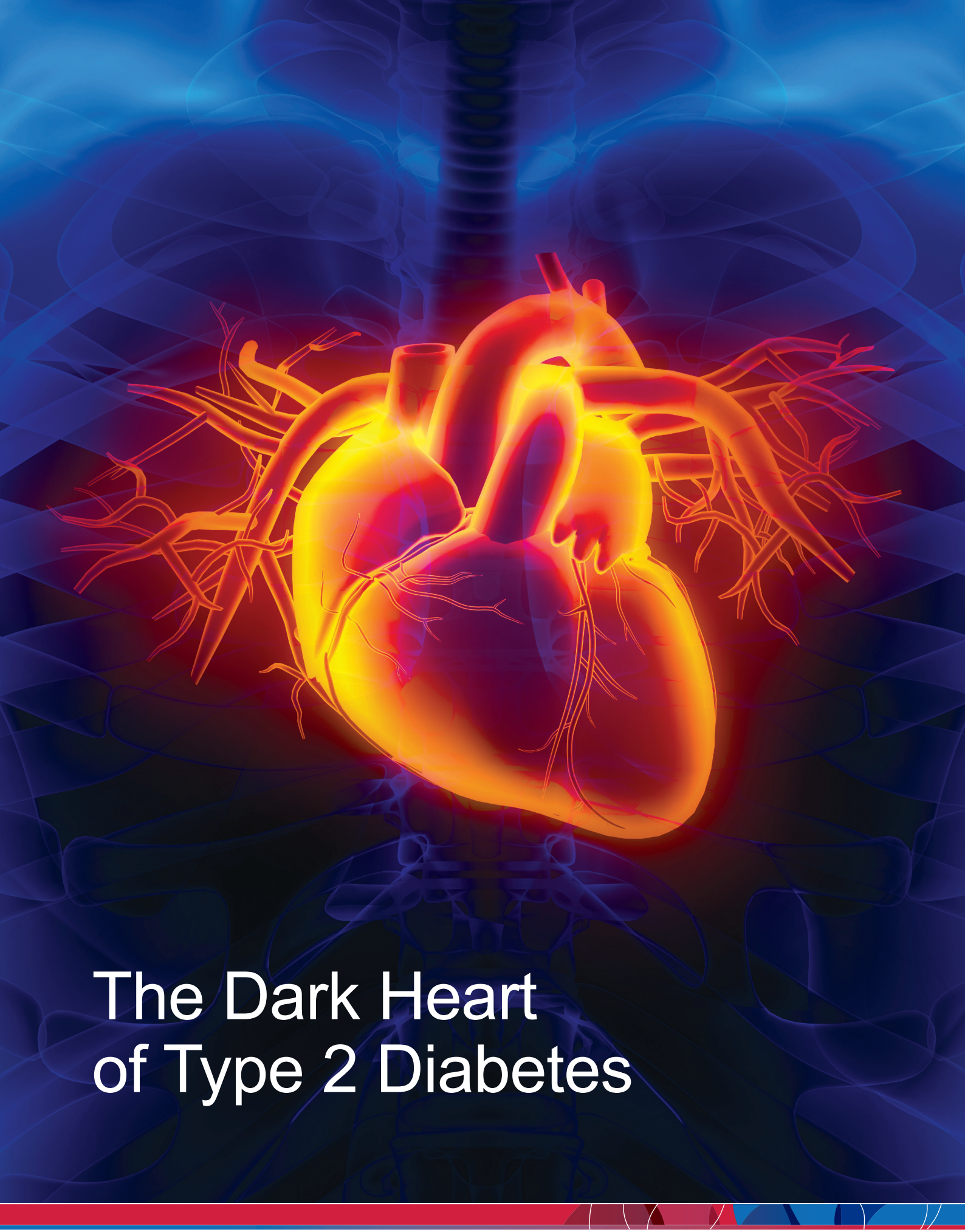


The Dark Heart of Type 2 Diabetes

Baker
HEART & DIABETES INSTITUTE

Contents

Executive Summary

Type 2 diabetes affects the health of more than 1.5 million Australians.

Lifetime risk of developing the condition is at least one in three, and it is now the fourth most common condition managed in general practice.

Much attention has been given to the prevalence, prevention and management of the microvascular complications of type 2 diabetes (nephropathy, neuropathy, and retinopathy). **The focus of this report is instead on diabetes as it relates to cardiovascular disease (CVD) – *the dark heart of diabetes.***

CVD is the most important complication of type 2 diabetes, accounting for not only the majority of its financial costs, but also a large proportion of the reduced health and reduced life expectancy in those with the condition.

Diabetes is also well recognised as an independent risk factor for all forms of CVD. The majority of patients (almost two in three) report concomitant CVD, and CVD remains the leading cause of death in people with type 2 diabetes.

Despite many years of improvements in therapies that lower blood glucose or address other CVD risk factors, and falling rates of cardiovascular deaths overall, diabetes continues to approximately double the risk of developing or dying from CVD. The risk is even more pronounced in women (type 2 diabetes erodes the gender associated protection against CVD), those with early-onset diabetes (before 40 years of age), and Indigenous Australians.

People with type 2 diabetes are unusually prone to dying from heart failure or sudden cardiac death. The likelihood of death from heart failure is elevated to the same level as from myocardial infarction, and sudden cardiac death is twice as common in those with type 2 diabetes as in those without the condition.

However, death from CVD is not inevitable in people with type 2 diabetes. This report outlines the multifactorial interventions that can significantly reduce cardiovascular risk and improve survival in those with established CVD.

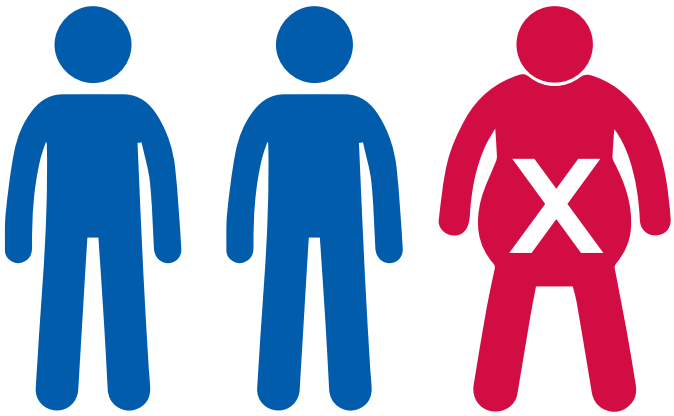
The Burden of Type 2 Diabetes

Today, diabetes affects the health of at least 1.5 million Australians.

Globally, over 400 million people have diabetes, with expectations that this figure will pass 600 million within 20 years[1]. It is anticipated that by 2025, at least one in every ten adults in Australia will have diabetes[1]. Of people aged 65 years and over, almost one in three will have diabetes.

Lifetime risk of developing type 2 diabetes is at least one in three[2,3]. Type 2 diabetes is most common in subgroups who are also at greatest risk of CVD including low socioeconomic status, the elderly, the obese and Indigenous Australians, in whom the lifetime risk for diabetes may exceed 50%[4,5].

Figure 1: The lifetime risk of diabetes now exceeds one in three[3]



Diabetes is now the 4th most common condition managed in general practice[6]. Not only are the numbers of consultations rising, but so is the complexity and cost of their care. Most people with diabetes have multiple co-morbidities, and are usually taking multiple medications. The overlap of diabetes with depression and other mental health conditions further exacerbates the complexity of its management.

The financial cost of diabetes to society is immense. The total annual cost of diabetes for medical care and government subsidies in Australia exceeds $10 billion. The contribution of complications of diabetes to this burden is substantial, as the presence and severity of diabetic complications increases the costs for an individual with diabetes by at least a factor of three[7].

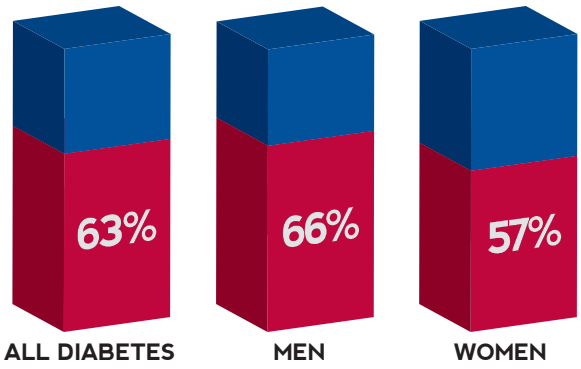
Cardiovascular Disease in Diabetes

Diabetes is a leading cause of preventable cardiovascular disease (CVD).

Diabetes is an independent risk factor for all manifestations of CVD. In particular, patients with type 2 diabetes experience rates of coronary heart disease (CHD), including angina pectoris, non-fatal and fatal myocardial infarction, and sudden cardiac death that are higher than in non-diabetic adults.

The burden of CVD among people with diabetes is substantial. Almost two in three adults with type 2 diabetes self-report CVD (Figure 2)[8].

Figure 2: The prevalence of self-reported CVD in adults with diabetes, by gender[8]



In Australian primary care, one in three patients seeing their GP have previously had a heart attack, stroke or have peripheral vascular disease[9]. Previously diagnosed diabetes is present in 28% of Australians admitted to hospital with an acute coronary syndrome[10], with a substantial additional proportion likely to have undiagnosed diabetes. Type 2 diabetes generates approximately one quarter of all referrals for coronary revascularisation[11].

Approximately 1-3% of individuals with type 2 diabetes experience a CHD event per year; this rate is approximately twice that in non-diabetic individuals. Moreover, these events occur at a younger age than in non-diabetic individuals. This increased risk in comparison to age and sex-matched controls is more pronounced in younger than older people and in women than men.

Type 2 diabetes mellitus has an adverse influence on the prevalence, severity and prognosis of CVD. In the AusDiab study of 11,247 participants from the general population across Australia, approximately 34% of all deaths over a 5-year period were due to CVD, of which two thirds occurred in people with either diabetes or prediabetes[12].

Diabetes is a significant risk factor for premature cardiovascular mortality, equivalent in magnitude to that observed in patients with a history of myocardial infarction or stroke[13]. However, many adults with diabetes also have CVD, in whom the combination of these conditions is associated with multiplicative mortality risk[13].

TABLE 1. The increased rate of CVD in diabetes is thought to reflect a cardiovascular pathology associated with:

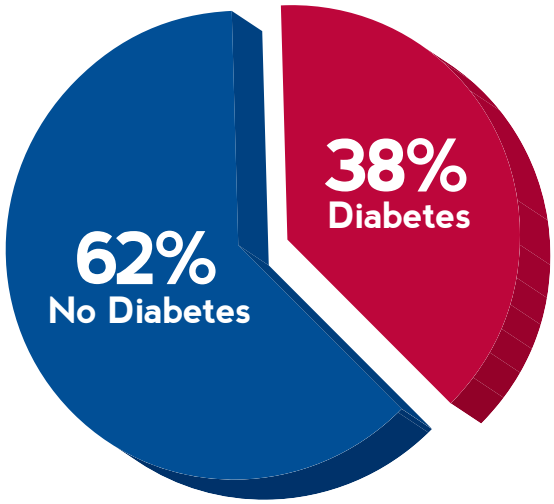
- Greater plaque burden
- Greater complexity of lesions
- Greater coronary calcification
- Greater extent of coronary ischaemia
- More diffuse disease
- More multi-vessel disease
- More significantly-affected vessels
- Fewer normal vessels
- Reduced coronary collateral recruitment
- Reduced coronary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

Heart Failure in Type 2 Diabetes

Diabetic individuals are unusually prone to heart failure (HF)[14].

HF is associated with reduced quality of life, more hospital admissions, longer admissions and more readmissions in patients with diabetes. One New South Wales snapshot audit showed that more than a third of acute admissions to hospital with heart failure involve a patient with diabetes[15].

Figure 3: Percentage of admssions with acute heart failure in which diabetes was a co-morbidity (adapted from ref 15)



CHF in diabetes often foreshadows a reduced life expectancy. Indeed, the presence of CHF may be considered the strongest risk factor for reduced survival in adults with type 2 diabetes and CVD[16].

CHF is now a leading cause of CVD death in adults with type 2 diabetes. For example, in a recent clinical trial conducted in people with type 2 diabetes and established CVD, the number of deaths due to heart failure was the same as the number due to myocardial infarction[17]. The rate of heart failure events now exceeds that of acute myocardial infarction in many of the diabetes medication trials[18].

Chronic heart failure (CHF) is a complex syndrome characterised by a collection of clinical characteristics and symptoms, many of which (e.g. dyspnoea and fatigue) may be readily confused with diabetes itself or other co-morbidities such as obesity.

Systolic heart failure or heart failure with reduced ejection fraction (HFrEF) is typically associated with CHD, cardiac ischemia and injury. The functional impact of muscle loss associated with CHD is generally more severe in diabetic patients, and those with diabetes are more likely to develop CHF following a myocardial infarction[19].

Beyond coronary artery disease, ischemia and infarction, diabetes has direct effects on myocardial function and structure with reduced compliance, impaired relaxation and increased filling pressures, despite normal ventricular contraction. This is known as **diastolic heart failure** or heart failure with preserved ejection fraction (HFpEF). HFpEF is now the most common presentation of heart failure in patients with type 2 diabetes, reflecting not only their diabetes but also co-morbid obesity, longstanding hypertension, cardiac remodelling and advanced age.

Atrial fibrillation (AF) also increases the risk of heart failure approximately 3-fold, and 42% of patients experiencing AF have heart failure at some point during their lifetime[20]. Atrial fibrillation is also associated with a 4- to 5-fold increased risk of ischemic stroke. AF is more common in adults with diabetes, chiefly due to cardiac stiffening[21].

Some medications commonly used in the treatment of diabetes may also increase patient risks from heart failure, including thiazolidinediones, moxonidine, dihydropyridine calcium channel blockers, itraconazole and some appetite suppressants[14].

Cardiovascular Death in Diabetes

In 2010 in adults aged 20-79 years, around five million deaths globally were attributable to diabetes, with at least half of these deaths attributable to CVD[1]. Having type 2 diabetes shortens life expectancy on average by 8.2 (6.7, 9.7) years for men and 9.1 (7.9, 10.4) years for women. Most of this is due to premature cardiovascular deaths[3].

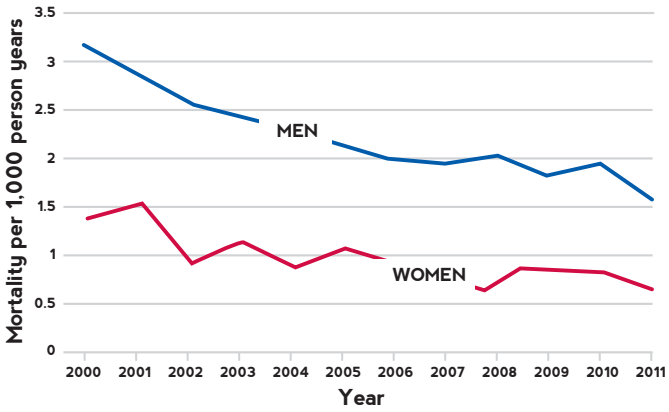
Death from CVD occurs more commonly and at a younger age in people with diabetes than among the non-diabetic population. Even after accounting for the increased blood pressure and dyslipidaemia associated with diabetes, the cardiovascular mortality in diabetes is approximately 2.5 times higher than in the age-gender matched non-diabetic population[12]. On average, the estimated loss of life expectancy associated with diabetes at age 50 years is 3 years as compared with adults without diabetes[22].

Women experience a relatively greater increase in their relative risk of death due to CVD associated with diabetes, as the gender-associated protection against CVD is lost in women with type 2 diabetes. Higher relative risks are also observed for younger adults, who, in the absence of diabetes, have low to no risk of CVD. However, having diabetes is associated with increased CVD mortality risks even in octogenarians.

Higher cardiovascular mortality in adults with diabetes is partly due to the increased frequency of cardiovascular events experienced by those with diabetes. In addition, cardiovascular events in adults with diabetes are associated with reduced early (30-day) survival[19].

The cardiovascular death rate among people with type 2 diabetes has substantially fallen over the last decade, in both men and women[23]. However, CVD remains responsible for just under a third of all deaths in people with diabetes.

Figure 4: CVD mortality trends in Australians with type 2 diabetes aged 40-60 years, by gender[23]



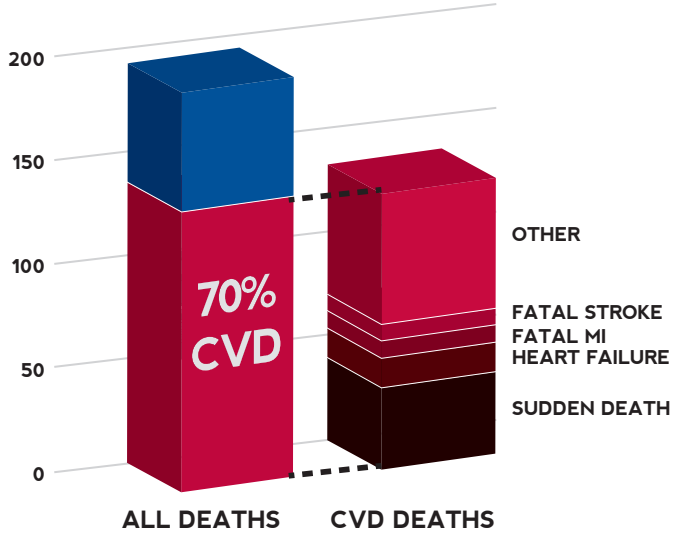
In the United Kingdom Prospective Diabetes Study, after 9 years of follow-up, fatal CVD events were 70 times more frequent than fatal microvascular complications[24].

Sudden Cardiac Death in Diabetes

Sudden cardiac death (SCD) is approximately twice as common in adults with type 2 diabetes when compared to non-diabetic individuals[25].

SCD may account for over half of all deaths from cardiovascular causes[17], especially in those with structural heart disease[25]. However, many people with type 2 diabetes die suddenly, despite no prior history of clinical heart disease. SCD is both their first and last cardiac event. While some of these sudden unexpected events may be a witnessed cardiac arrest, many deaths are unseen or occur at night (sudden nocturnal death).

Figure 5: Causes of death in placebo-treated patients with type 2 diabetes and established CVD from the EMPA-REG study of empagliflozin[17]



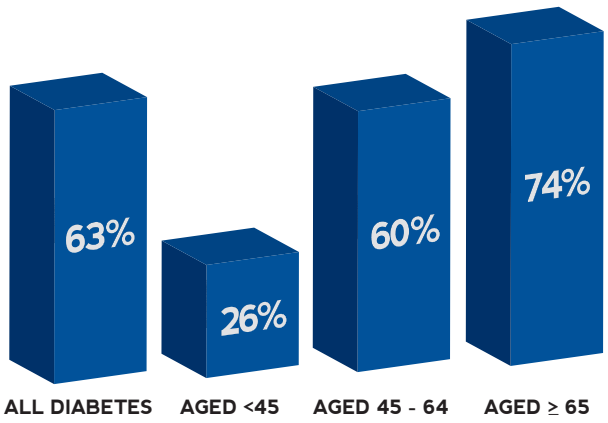
The association between SCD and diabetes may be partly mediated by the greater (and sometimes occult) burden of CVD and heart failure in patients with type 2 diabetes. However, autonomic dysfunction, QTc prolongation, electrolyte disturbances, inflammation, oxidative and metabolic stress in diabetes may also increase arrhythmogenesis[26]. Other co-morbid conditions may also contribute to this risk, including obstructive sleep apnoea, renal impairment and mental illness.

Hypoglycaemia is a latent risk factor for sudden death and arrhythmia, beyond the immediate effects of low blood sugar on brain function[27]. Since hypoglycaemia may exacerbate myocardial ischemia and may cause dysrhythmias, it follows that strategies that reduce the risk of this adverse event are preferred in patients with type 2 diabetes at high CVD risk[28].

CVD in Special Populations

Elderly (>70 years old) people with type 2 diabetes have a high rate of CVD, and it is their leading cause of death. At least three in every four adults with diabetes over 75 self-report CVD[29]. At the same time, many older patients have reduced quality of life, shorter life expectancy, more co-morbidities and a higher risk of side-effects from interventions, altering the risk-benefit ratios for such interventions. It should also be noted that, apart from blood pressure interventions, the elderly are under-represented in clinical trials, and therefore any extrapolation (of benefits as well as risks) should be done cautiously.

Figure 6: The prevalence of self-reported CVD in adults with diabetes, by age[8]



Aboriginal and Torres Strait Islander people not only have an increased risk of type 2 diabetes, but those with type 2 diabetes also have a higher incidence of CVD and death from CVD, moreover at a comparably younger age than in non-Indigenous Australians. While this partly reflects reduced access to health services aimed at preventing and treating CVD, Indigenous patients are no more likely to be receiving preventive therapy than non-Indigenous patients presenting at the same practice, despite the fact that their age-standardised risk for CVD is substantially higher[30].

Younger adults with type 2 diabetes should anticipate a longer life expectancy. However, these patients often carry an increased risk for diabetic complications including CVD. A number of different factors may contribute to the excess risk, including co-morbid obesity, hypertension, dyslipidaemia, insulin resistance, sub-optimal glucose control, and ethnic and socioeconomic factors. In addition, the reductions in cardiovascular mortality over the last decade observed in middle-aged and older adults with diabetes have not been seen in those aged under 40 years[23]. These findings at a national level are supported by recent data from Sydney showing that the effect of diabetes on mortality is proportionately 2-3 times greater in those with diabetes onset before age 40, compared to those with older onset[31].

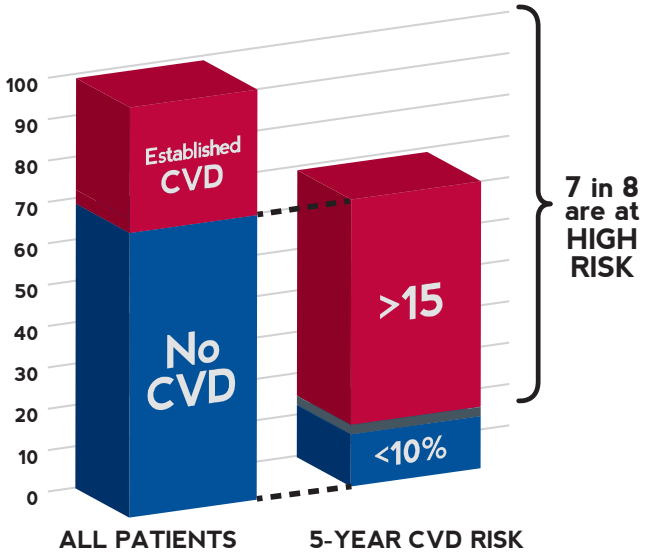
Chronic Kidney Disease (CKD) is an independent risk factor for CVD in patients with type 2 diabetes. The presence and severity of albuminuria and/or renal impairment predicts incident CVD and its outcomes[32]. At the same time, many patients with CKD have a reduced quality of life, shorter life expectancy, more co-morbidity and a higher risk of side-effects, which alters the risk-benefit ratio for interventions.

Assessing/Screening CVD in Diabetes

Calculation of absolute CVD risk through comprehensive risk factor assessment is worthwhile in people with type 2 diabetes without CVD. However, formal assessment of CVD risk is not always necessary, as the absolute risk of CVD is obviously high (>15% over 5 years) in many cases, because of the conglomeration of diabetes with one or more other high-risk states (i.e. age > 60 years, Indigenous Australians, microalbuminuria or estimated glomerular filtration rate [eGFR] <45 ml/min). Risk assessment is also unnecessary in patients with established CVD.

Approximately one third of patients with type 2 diabetes in primary care do not have CVD and do not have clear markers of cardiovascular risk. In this setting, formal (numerical) estimation of absolute cardiovascular risk is warranted. This not only informs patients of their risks but also quantitates the absolute benefits that could be achieved from interventions. Risk calculators that combine a number of key factors to determine the absolute risk of CVD are widely available, including an **Australian 'at risk calculator'**. The presence of any additional cardiovascular risk factors, beyond those already included in the risk calculators, should also be taken into account (e.g. atrial fibrillation, CKD, depression, Indigenous Australians, socioeconomic disadvantage) in categorising the risk status of any individual patient.

Figure 7: The distribution of CVD risk in patients with type 2 diabetes in Australian General Practice: NEFRON study (adapted from ref 33)



CVD is often silent in patients with type 2 diabetes. While symptoms are a reliable indicator of clinically-significant CVD in people with diabetes, the absence of symptoms does not exclude it. The survival of patients with a silent myocardial infarction may be as poor as those who have had a clinical event[34].

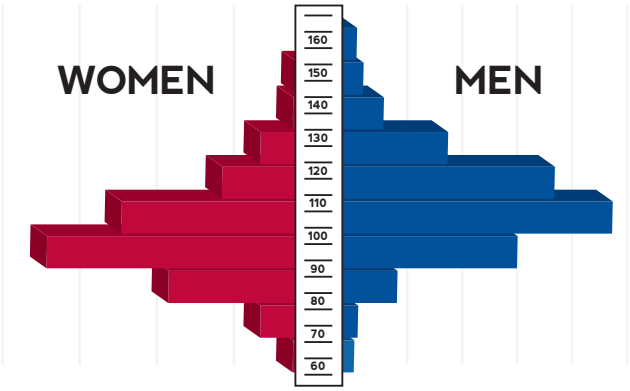
Screening for subclinical CVD (e.g. resting electrocardiogram, exercise stress testing, stress echo) is not generally recommended in people with type 2 diabetes without any cardiac symptoms. This is for two reasons. First, patients with sufficient cardiovascular risk to warrant screening should already be intensively medically managed. Second, trials have failed to show that such screening tests result in changes in management leading to a reduction in cardiac event rates.

Coronary artery calcium (CAC) scanning may be a useful marker of coronary artery disease[35]. In particular, a score of zero generally excludes significant CVD risk. However, this test is not currently subsidised by Medicare.

Diet, Lifestyle and Education for CVD

In adults with type 2 diabetes, diet and lifestyle contribute significantly to their cardiovascular risk. Many people with type 2 diabetes are overweight and obese, have a low level of physical activity, and/or have a poor diet, including insufficient consumption of fruit and vegetables. Approximately 12% of people with type 2 diabetes in Australia continue to smoke[4].

Figure 8: The distribution of waist circumference in patients with type 2 diabetes in Australian General Practice[36]



Optimal nutrition, moderate weight reduction and increased physical activity are recommended to reduce the incidence and improve outcomes from CVD in adults with type 2 diabetes. However, while there are many benefits of lifestyle change, the Look AHEAD study showed that substantial lifestyle change did not produce a reduction in risk of cardiovascular morbidity or mortality in people with type 2 diabetes who were obese (average BMI 36 kg/m^2)[37].

Weight loss of 5-10% is worthwhile as over 95% of those with type 2 diabetes are overweight or obese, many extremely so.

Undertaking regular physical activity of at least 30 minutes of moderate-intensity on most, if not all, days of the week (i.e. 150 minutes/week minimum) is recommended for adults with type 2 diabetes. This amount can be accumulated in shorter bouts of 10 minutes' duration and can be built up over time. Additional benefits may be accrued from additional activity, but any increase in physical activity towards these goals may be beneficial.

Smoking cessation is an essential means to lower the risk of CVD in smokers with type 2 diabetes[38].

Co-morbid psychological stress, anxiety and depression are significantly associated with CHD and its outcomes[39]. Interventions to address these important issues may modify cardiovascular risk factors and quality of life. However, an unambiguous impact on cardiovascular outcomes remains to be established.

An action plan for what to do in a cardiovascular emergency is important for all those at increased cardiovascular risk. Given the frequency of CVD in diabetes, all individuals with type 2 diabetes should be made familiar with the warning signs of a heart attack, and have a proactive response plan that includes an early and appropriate ambulance call. Patient education can result in earlier recognition and presentation after an acute coronary event.

Primary Prevention of CHD in Diabetes

The rates of primary acute coronary events in adults with type 2 diabetes have declined over the last decade. This may be partly attributable to the increasing use of drugs to lower cholesterol and blood pressure in primary prevention.

Medicines that lower low density lipoprotein (LDL) cholesterol (e.g. statins, ezetimibe) reduce morbidity and mortality from CVD in people with type 2 diabetes at high cardiovascular risk, and the benefit is proportional to the degree of LDL cholesterol lowering[40]. The cardiovascular benefits are also long-lasting[41].

Recognising the high cardiovascular risk of patients, statins are the most common class of drug used for the management of type 2 diabetes in Australian primary care. Up to three quarters of Australian patients with type 2 diabetes are prescribed a statin, including two thirds of patients without clinical CVD[33]. This is despite the fact that most patients with diabetes do not have overtly elevated serum LDL cholesterol[33], as statin therapy should be considered in anyone with type 2 diabetes at high cardiovascular risk, regardless of baseline cholesterol levels[42].

Medicines that lower remnant cholesterol (e.g. fibrates) may have cardiovascular benefits in addition to standard therapy with statins in patients with elevated triglyceride levels (generally >2.3 mmol/L)[42].

Hypertension is a key risk factor for CHD in patients with type 2 diabetes, and is a logical target for the primary prevention of CHD. The use of medicines to achieve and maintain optimal blood pressure levels is able to reduce the incidence of cardiovascular events and cardiovascular mortality in people with type 2 diabetes at high cardiovascular risk. An appropriate target for most patients with diabetes is <140/90 mmHg, with lower targets considered for younger people, those with proteinuria and those at high risk of stroke, as long as the treatment burden is not high[43].

Some trials have suggested that agents that reduce activation of the renin-angiotensin aldosterone stream (RAAS, e.g. angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) have additional advantages over other antihypertensive strategies[44]. In practice, however, achieving treatment targets invariably requires multiple antihypertensive agents.

Accurate assessment of achieved blood pressure control is an important consideration given the importance of hypertension in the development of progression of CVD in diabetes. Standard in-clinic blood pressure poorly reflects ambient BP levels. Additional tests including 24-hour ambulatory blood pressure monitoring and home blood pressure monitoring may have advantages in detecting **masked or uncontrolled hypertension** in patients with diabetes[45].

Intensification of glucose control in patients with type 2 diabetes at increased cardiovascular risk may have long-term benefits on incident cardiovascular events and cardiovascular death[46]. This is known as metabolic karma or the legacy effect. Glucose lowering has no clear benefits in the short and medium term on cardiovascular outcomes in patients without CVD[47].

Antithrombotic therapy with low-dose aspirin has a small to non-significant effect (<10% risk reduction) on the risk of CHD events in diabetic patients who are clinically free of CVD (i.e. in primary prevention). Nonetheless, guidelines recommend that low-dose aspirin (75–150 mg/d) can be considered for the primary prevention of CVD in adults with type 2 diabetes who are at increased CVD risk (10 year risk of cardiovascular events ≥ 10%) and who are not at increased risk for bleeding[48].

Strategies to improve adherence are also valuable, as polypharmacy, high costs, complex dosing regimens and multiple practitioners involved in care, increase the risk of non-compliance in complicated patients with diabetes. Practical interventions include fixed-dose combinations, pre-packaging, improved education, communication, coordination and continuity of care.

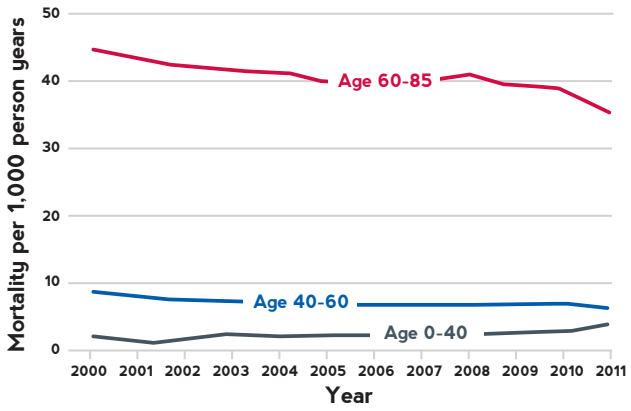
TABLE 2. Strategies to improve adherence

- Fixed-dose combination drugs
- Patient education, support and follow-up
- Reduced drug regimen complexity (timing, dosing, frequency, etc.)
- Choosing strategy with fewest real or perceived side effects

Secondary Prevention of CHD in Diabetes

The frequency of death from CHD has declined significantly over the last several decades[23,49]. This may be partly due to better treatment of patients with CHD, including aggressive lipid and blood pressure lowering, anti-thrombotic therapy and effective coronary interventions.

Figure 9: Mortality trends in Australians with type 2 diabetes, by age[23]



Medicines that lower LDL cholesterol (e.g. statins, ezetimibe) reduce morbidity and mortality from CVD in people with type 2 diabetes with CHD, proportional to the degree of LDL cholesterol lowering, and irrespective of baseline LDL cholesterol levels[50,51]. The use of more potent statins and titration to the maximal tolerated dose to achieve greater lowering of LDL cholesterol is often appropriate in adults with diabetes and CVD, given their high level of risk[50,51].

Lowering of blood pressure in adults with type 2 diabetes and established CHD reduces the risk of further cardiovascular events and cardiovascular death, and should be undertaken unless contra-indicated or clinically inappropriate[50]. In the absence of hypertension, blood pressure lowering may still have cardiovascular benefits in patients with type 2 diabetes and established CHD, including lowering the risk of stroke and CKD[43].

Some antihypertensive agents may have specific advantages in patients with established CHD. For example, adults with a prior acute myocardial infarction may benefit from long-term treatment with beta blockers[50]. RAAS blockade with ACE inhibitors or ARBs may also reduce cardiovascular events and incident heart failure in adults with diabetes and CHD[50].

Intensification of glucose control in patients with type 2 diabetes with established CVD has no clear benefits in the short and medium term on cardiovascular outcomes, including cardiovascular death[47]. However, recent trials with sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP1) receptor agonists suggest additional cardiovascular benefits beyond glucose lowering may be conveyed by these treatment strategies[17,52,53].

Antiplatelet therapy is effective in reducing cardiovascular morbidity and mortality in patients with a prior myocardial infarction or stroke. All adults with type 2 diabetes and prior coronary events should receive low dose aspirin or other platelet inhibitor, such as clopidogrel (if intolerant of aspirin) unless there is a contraindication (e.g. significant bleeding risk)[42,50]. Adults with an acute coronary event or coronary stent should receive combination therapy with low-dose aspirin and another antithrombotic agent (e.g. clopidogrel, prasugrel or ticagrelor) for 12 months[42,50].

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are a crucial component of the management of symptomatic disease. However, since patients with diabetes often have multi-vessel disease, CABG is often preferred over standard PCI[54], although the appropriateness of either intervention is highly individual. Drug eluting coronary stents may also offer particular advantages for diabetic patients[54].

Guidelines and Resources

- RACGP Guideline for the Management of Type 2 Diabetes (2016-2017)[42]
- NHMRC Guidelines for secondary prevention of CVD in patients with type 2 diabetes[50]
- AUSDRISK calculator[55]
- AIHW reports[4,5,29]

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Acknowledgements

Authors

Professor Jonathan Shaw

Professor Jonathan Shaw MD is the Deputy Director (Clinical and Population Health) of the Baker Institute and practises as a diabetes specialist at the Institute's clinics. He has research interests in the epidemiology of diabetes and its complications.

As well as authoring over 350 peer-reviewed scientific papers and 35 book chapters, Professor Shaw is a Chief Investigator on the AusDiab Study, the largest population-based study in Australia examining the natural history of diabetes, pre-diabetes, heart disease, and kidney disease.

Professor Merlin Thomas

Professor Merlin Thomas MBChB, PhD, FRACP heads the Biochemistry of Diabetes Complications laboratory in the Department of Diabetes at Monash University, Melbourne.

A clinician scientist, he works with patients with diabetes and their doctors, as well as performing research in experimental models of diabetic complications. He is also author of *Understanding Type 2 Diabetes and an author of The CSIRO and Baker IDI Diabetes Diet and Lifestyle Plan.*

Associate Professor Dianna Magliano

Associate Professor Dianna Magliano B.App Sci(Hons), MPH, PhD is an epidemiologist at the Baker Institute whose work focuses on the causes and consequences of diabetes.

Associate Professor Magliano is the President of the International Diabetes Epidemiology Group, an editor at *Diabetes Research and Clinical Practice* and is on *The Lancet Diabetes and Endocrinology* advisory panel.

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Baker Heart and Diabetes Institute

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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