INTERNAL MEDICINE JOURNAL

doi:10.1111/imj.16455

CLINICAL PERSPECTIVE

Preventing diabetes complications

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Key words
diabetes, macrovascular complications, microvascular complications, cardiovascular disease, glycaemic control.

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Received 15 November 2023; accepted 23 May 2024.

The key aim of diabetes management is to prevent complications, which are a major cause of morbidity and mortality. At an individual level, people with diabetes are less likely than they were several decades ago to experience classical macrovascular and microvascular complications as a result of improvements in modifiable cardiovascular risk factors and preventive healthcare. However, a significant burden of diabetes complications persists at a population level because of the increasing incidence of diabetes, as well as longer lifetime exposure to diabetes because of younger diagnosis and increased life expectancy. Trials have shown that the most effective strategy for preventing complications of diabetes is a multifactorial approach focussing simultaneously on the management of diet, exercise, glucose levels, blood pressure and lipids. In addition to the cornerstone strategies of addressing diet, exercise and lifestyle measures, the introduction of newer glucose-lowering agents, including sodium-glucose transport protein 2 inhibitors and glucagon-like peptide-1 agonists, have brought about a paradigm shift in preventing the onset and progression of complications of type 2 diabetes, particularly cardiovascular and renal disease. The improvement in rates of classical complications of diabetes over time has been accompanied by a growing awareness of non-traditional complications, including non-alcoholic fatty liver disease. These emerging complications may not respond to a glycaemic-centred approach alone and highlight the importance of foundational strategies centred on lifestyle measures and supported by pharmaceutical therapy to achieve weight loss and reduce metabolic risk in patients living with diabetes.

Introduction

Diabetes complications are responsible for much of the burden associated with diabetes both on an individual and a healthcare system level. Recent decades have seen large increases in the number of people diagnosed with diabetes as well as longer life expectancy because of declining cardiovascular mortality, leading to an overall increase in diabetes prevalence.[1] Published data from high-income countries indicate large reductions in the classical complications of diabetes – likely because of improvements in the management of modifiable cardiovascular risk factors, including glycaemia, blood pressure, lipids and smoking – but these improvements are offset by the sheer number of people living with diabetes. In the United States, for example, the rates of acute myocardial infarction (MI), lower-extremity amputation, end-stage renal failure (ESRF), stroke and death from hyperglycaemic crisis declined dramatically between 1990 and 2010. Calculations per unit of the general population, however, reflect the rising prevalence of diabetes: while declines continued in the rates of MI and hyperglycaemic mortality, there was no change in the rates of amputation or stroke, and the rate of ESRF nearly doubled.[2]

The rising incidence of diabetes is particularly significant in younger people, who are expected to have longer lifetime exposure to diabetes and, therefore, a higher risk of developing complications. The increasing worldwide prevalence of young-onset type 2 diabetes (T2D) is particularly concerning as youth with T2D have a higher prevalence of complications than both their same-aged counterparts with type 1 diabetes (T1D) and those with later-onset T2D.[3,4] At any given time, most people with diabetes do not have any diabetes-related

Funding: None.
Conflict of interest: None.

complications, as shown in Australian population-level data.[5] This means that for most patients with diabetes, the opportunity exists to prevent the onset of complications.

Classical complications

Conventionally, complications of diabetes have been divided into macrovascular – including ischaemic heart disease, cerebrovascular disease and peripheral vascular disease – and microvascular – including diabetic nephropathy, retinopathy, peripheral neuropathy, autonomic neuropathy and gastroparesis. Other complications such as diabetic foot disease and erectile dysfunction have a combined macro- and microvascular aetiology. In combination, these complications are responsible for significant morbidity and mortality in people with diabetes. The observational DISCOVER study found a global prevalence of 18.8% for microvascular diabetes complications and 12.7% for macrovascular complications.[6]

Historically, the main focus of risk reduction was on lowering blood glucose levels, until the landmark UKPDS trial, which followed participants with newly diagnosed T2D, showed disappointing results from intensive glycaemic control alone on the reduction of cardiovascular complications.[7,8] The approach to risk reduction in diabetes has since broadened, as the benefits of treating hypertension and dyslipidaemia were demonstrated in trials, along with the emergence of specific agents for cardiovascular and renal protection. It is now well established that the most effective strategy to reduce diabetes complications is a multifactorial approach (Fig. 1).

Lifestyle intervention

Lifestyle modification focussing on balanced nutrition, physical activity and smoking cessation is universally recommended for people with diabetes. The Look AHEAD trial examined the effects of an intensive lifestyle intervention – involving dietary caloric restriction and increased physical activity – on cardiovascular mortality, non-fatal MI, non-fatal stroke and hospitalisation for angina in people with T2D. Although the intervention produced greater improvements compared to standard of care in weight, waist circumference, HbA1c, blood pressure and most lipids, these changes did not translate to a significant reduction in cardiovascular outcomes over nearly 10 years of follow-up, and the trial was ceased early on the basis of a futility analysis.[9] The smaller Steno-2 study, on the other hand, showed that lifestyle intervention in addition to glycaemic and blood pressure control in people with T2D and albuminuria resulted in a 53% reduction in a composite outcome of cardiovascular death, MI, stroke, revascularisation and lower-extremity amputation.[10]

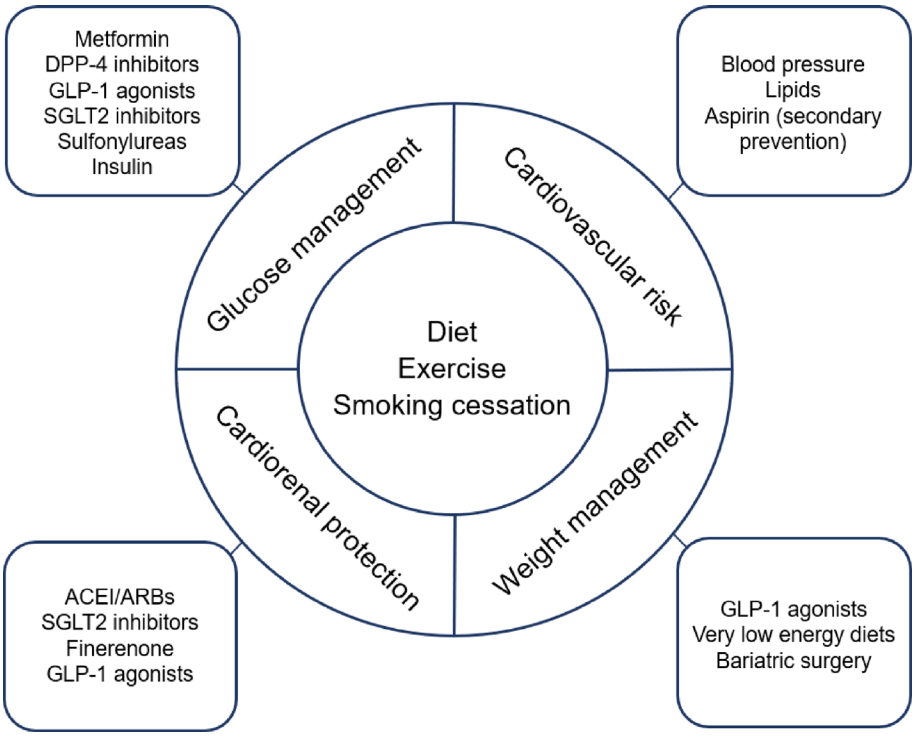

Figure 1 Multifactorial aspects of diabetes management and prevention of complications.

Current American Diabetes Association (ADA) guidelines recommend a combination of dietary modification, physical activity and behavioural strategies to achieve and maintain at least 5% weight loss for most people with T2D and overweight or obesity, although weight loss interventions must always be individualised.[11] At least 150 min per week of moderate-intensity aerobic activity, spread over at least 3 days of the week, is recommended for most adults with T2D.[12]

Glycaemic control

Intensive glycaemic control, once thought to be the cornerstone of preventing macrovascular complications, has been the subject of conflicting data in recent decades. Initial analyses of the DCCT and UKPDS trial, evaluating the effect of intensive treatment in T1D, demonstrated significant improvements in microvascular complications but only non-significant benefits in macrovascular disease.[7,13] The subsequent ADVANCE trial and VADT similarly found no significant cardiovascular risk reduction with intensive glucose-lowering treatment.[14,15] The results of the ACCORD trial were more concerning and found that intensive glycaemic control increased all-cause mortality by 22%, largely driven by cardiovascular mortality, resulting in early cessation of the trial.[16]

Early data on the association between intensive glycaemic control and microvascular complications were much more encouraging. In initial DCCT data, with a mean follow-up of 6.5 years, intensive treatment reduced incident retinopathy risk by 76% and risk of progression of pre-existing retinopathy by 54%. The risk of albuminuria was reduced by 34% and 56% in the primary and secondary prevention cohorts respectively, whereas the risk of neuropathy was reduced by 69% and 57%.[13]

Over long-term follow-up, the so-called legacy effect of intensive glycaemic control became apparent, with a significant reduction in major cardiovascular events observed in 10-year follow-up of the UKPDS cohort and 30-year follow-up of the DCCT/EDIC cohort.[17,18] Although differences in HbA1c had merged between the two DCCT groups, a 32% reduction in major cardiovascular events was seen after three decades in subjects who had been in the intensive treatment group compared to their counterparts in the conventional treatment group.[18] Follow-up studies in the DCCT/EDIC cohort also demonstrated sustained improvements in the onset and progression of retinopathy, nephropathy and peripheral and autonomic neuropathy in participants who had received intensive treatment.[19,20] In the UKPDS cohort, a 37% reduction in any microvascular disease at 10 years follow-up was seen for every 1% decrement in HbA1c achieved in the initial trial period.[21]

Zoungas *et al.* demonstrated in a meta-analysis that intensive glycaemic control reduced the risk of a composite renal outcome by 20% and a composite retinal outcome by 13%, though there was no risk reduction for neuropathic events.[22] A Cochrane review has shown that tighter glycaemic control prevents the development of neuropathy in T1D, but the benefits in T2D are less significant.[23] Focusing on cardiovascular outcomes, a meta-analysis of 14 randomised clinical trials (RCTs) comparing intensive glycaemic control with conventional therapy in T2D suggested a modest benefit in the risk of non-fatal MI with a relative risk reduction of 15%. There was no significant effect on the risk of all-cause or cardiovascular mortality, whereas there was a 30% increase in the relative risk of severe hypoglycaemia.[24]

Glycaemic targets should always be individualised, but a target HbA1c of less than 7.0% (53 mmol/mol) is appropriate for most patients with diabetes if it can be safely achieved without excessive risk of hypoglycaemia.[25] For people using continuous glucose monitoring, general targets include >70% of the time in range (3.9–10.0 mmol/L), <4% of the time below range and <25% of the time above range; tighter targets are used in pregnancy and looser targets may be appropriate for those at high risk of hypoglycaemia (Table 1).[25,26]

SGLT2 inhibitors

The introduction of sodium-glucose transport protein 2 (SGLT2) inhibitors into clinical use has resulted in a major paradigm shift in cardiovascular risk reduction in T2D. Major cardiovascular outcome trials using SGLT2 inhibitors are summarised in Table 2. The EMPA-REG OUTCOME trial, which enrolled participants with T2D and high baseline cardiovascular risk, demonstrated significant reduction in a composite primary outcome of

Table 1 General glycaemic targets for people with diabetes

	HbA1c	CGM
Most non-pregnant adults	<7% (53 mmol/mol)	TIR > 70% TAR < 25% TBR < 4%
Older adults or those at high risk of hypoglycaemia	<8% (64 mmol/mol)	TIR > 50% TBR < 1%

Achievement of targets must always be balanced against risk of hypoglycaemia. Lower targets may be appropriate in select patients, for example younger patients with few comorbidities and long life expectancy.

CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range.

Table 2 Major cardiovascular outcome trials of SGLT2 inhibitors[27,78–80]

Trial	EMPA-REG OUTCOME (2015)	CANVAS (2017)	DECLARE-TIMI 58 (2019)	VERTIS CV (2020)
Drug versus placebo	Empagliflozin 10 mg or 25 mg	Canagliflozin 100–300 mg	Dapagliflozin 10 mg	Ertugliflozin 5 mg or 15 mg
Size, *n*	7020	10 142	17 160	8246
Median follow-up, years	3.1	2.4	4.2	3.0
Key inclusion criteria	T2D History of CVD	T2D History of CVD or age ≥50 with at least two CV risk factors	T2D History of CVD or age ≥55 (males) or ≥60 (females) with at least one CV risk factor	T2D History of CVD
Primary composite CV outcome, HR (95% CI)†	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.97 (0.85–1.11)
CV death, HR (95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.77 (1.11)
MI, HR (95% CI)	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	1.04 (0.86–1.26)
Stroke, HR (95% CI)	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	1.06 (0.82–1.37)

†Primary outcome in all trials was a composite of CV death, non-fatal MI and non-fatal stroke.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes.

cardiovascular death, MI, stroke and hospitalisation for angina, in participants randomised to receive empagliflozin. This composite effect was driven mainly by benefits on cardiovascular and all-cause mortality.[27] A 2022 meta-analysis of 13 trials found that SGLT2 inhibitors reduced the relative risk of cardiovascular death by 14% in people with diabetes.[28] A clear benefit has also been shown in preventing hospitalisation for heart failure, in people with either reduced or preserved ejection fraction, regardless of diabetes status, with a relative risk reduction of 23% in a meta-analysis of major trials using empagliflozin and dapagliflozin.[29]

SGLT2 inhibitors have brought about a similar paradigm shift in the delay of the development and progression of microvascular complications, particularly nephropathy. The renoprotective benefits of SGLT2 inhibitors first became apparent in secondary analyses of cardiovascular outcome trials that demonstrated a slowing of renal disease progression; several dedicated trials focussing on primary renal outcomes then followed (Table 3).[30] CREDENCE, comparing canagliflozin with placebo in people with T2D and nephropathy, demonstrated a 30% risk reduction in the progression of renal disease, followed by similar results in RCTs using dapagliflozin and empagliflozin.[31–33] In a meta-analysis of 13 RCTs, SGLT2 inhibitors reduced the risk of chronic kidney disease (CKD) progression by 38% and the risk of acute kidney injury by 21% in participants with diabetes.[28]

SGLT2 inhibitors are currently recommended for patients with T2D and established cardiovascular disease

Table 3 Major renal outcome trials of SGLT2 inhibitors[31–33]

Trial	CREDENCE (2019)	DAPA-CKD (2020)	EMPA-KIDNEY (2023)
Drug versus placebo	Canagliflozin 100 mg	Dapagliflozin 10 mg	Empagliflozin 10 mg
Size, *n*	4401	4304	6609
Median follow-up, years	2.6	2.4	2.0
Key inclusion criteria	T2D eGFR 30–90 mL/min/1.73 m^2 uACR 300–5000 Maximally tolerated RAS blockade	eGFR 25–75 mL/min/1.73 m^2 uACR 200–5000 Maximally tolerated RAS blockade	eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 with uACR >200 Maximally tolerated RAS blockade
Proportion with diabetes, %	100%	68%	46%
Primary composite renal outcome, HR (95% CI)	0.70 (0.59–0.82)†	0.61 (0.51–0.72)‡	0.86 (0.78–0.95)§
ESRF, HR (95% CI)	0.68 (0.54–0.86)	0.64 (0.50–0.82)	0.73 (0.59–0.89)¶

†Primary outcome of CREDENCE: ESRF, doubling of serum creatinine, renal or CV death.
‡Primary outcome of DAPA-CKD: ESRF, sustained decline in eGFR ≥50% from baseline, renal or CV death.
§Primary outcome of EMPA-KIDNEY: ESRF, sustained decline in eGFR to ≤10 or ≥40% from baseline, renal or CV death.
¶Includes ESRF or CV death.
CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRF, end-stage renal failure; HR, hazard ratio; RAS, renin-angiotensin system; T2D, type 2 diabetes; uACR, urinary albumin-to-creatinine ratio.

or albuminuria, in the absence of contraindications. The EASE and DEPICT-2 trials have shown the glycaemic benefits of adjunctive therapy with empagliflozin and dapagliflozin, respectively, in adults with T1D[34,35]; however, their use in T1D remains controversial given the risk of diabetic ketoacidosis.[36] Despite these concerns, there is a growing movement to support the off-label use of SGLT2 inhibitors in carefully selected people with T1D for their metabolic, cardiovascular and renal benefits.[37,38]

GLP-1 agonists

Glucagon-like peptide-1 (GLP-1) agonists, such as SGLT2 inhibitors, have shown significant benefits in both glycaemic control and cardiovascular risk in people with T2D (major trials summarised in Table 4). A meta-analysis of eight trials demonstrated a 14% reduction in major cardiovascular events with GLP-1 agonist treatment.[39] Similar to SGLT2 inhibitors, *post hoc* analyses of cardiovascular outcome trials using GLP-1 agonists have suggested renal benefits, although trials focussing on renal primary outcomes are yet to be reported. In a secondary analysis of the REWIND RCT comparing dulaglutide with placebo, for example, a 15% risk reduction was seen in a composite renal outcome.[40]

Data on the use of GLP-1 agonists in T1D are limited. The largest RCTs, ADJUNCT ONE and TWO, found that the addition of liraglutide to insulin therapy reduced HbA1c, insulin requirements and body weight,[41,42] but effects on the risk of complications have not yet been evaluated in T1D.

A large meta-analysis conducted by Palmer *et al.* evaluated 764 RCTs comparing SGLT2 inhibitors or GLP-1 agonists with placebo or standard of care in people with T2D. Both classes reduced cardiovascular mortality in a similar fashion, with relative risk ratios of 0.84 and 0.88 respectively. Similar effect sizes were seen between classes for non-fatal MI, but GLP-1 agonists appeared to reduce the risk of non-fatal stroke, whereas SGLT2 inhibitors did not. A similar reduction in the rate of ESRF was seen between both classes, and neither class had a significant effect on retinal or neuropathic outcomes.[43]

Blood pressure

The cardiovascular benefits of antihypertensive therapy in people with T2D and hypertension have been well established.[8,44] A significant reduction in cardiovascular mortality and a composite of macro- and microvascular events was seen in the ADVANCE trial, in which participants were treated with a fixed-dose combination of an angiotensin-converting enzyme (ACE) inhibitor and diuretic.[45] The UKPDS trial involved randomisation of participants with T2D to tight or conventional blood pressure control using captopril or atenolol. Each 10–mmHg decrement in mean systolic blood pressure was associated with 11% and 18% reductions in the risk of MI and stroke respectively.[21] Subsequent meta-analyses have similarly shown that cardiovascular benefits increase as systolic blood pressure decreases,[46,47] although the optimal blood pressure targets remain uncertain. In the ACCORD trial, intensive antihypertensive therapy targeting a systolic blood pressure below 120 mmHg, compared to a target of 130–140 mmHg, did not result in any benefit in the primary composite outcome of cardiovascular death, non-fatal MI and non-fatal stroke. The absolute risk of stroke was reduced by 1% in the intensive therapy group, but this was

Table 4 Major cardiovascular outcome trials of GLP-1 agonists[40,81–83]

Trial	LEADER (2016)	SUSTAIN-6 (2016)	REWIND (2019)	AMPLITUDE-O (2021)
Drug vs placebo	Liraglutide 0.6–1.8 mg	Semaglutide 0.5–1 mg	Dulaglutide 1.5 mg	Efpeglenatide 4–6 mg
Size, *n*	9340	3297	9901	4076
Median follow-up, years	3.8	2.1	5.4	1.8
Key inclusion criteria	T2D High CV risk	T2D	T2D History of CVD or age ≥60 with at least CV risk factors	T2D History of CVD or at least one CV risk factor
Primary composite CV outcome, HR (95% CI)†	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.88 (0.79–0.99)	0.73 (0.58–0.92)
CV death, HR (95% CI)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.91 (0.78–1.06)	0.72 (0.50–1.03)
MI, HR (95% CI)	0.86 (0.73–1.00)	0.74 (0.51–1.08)‡	0.96 (0.79–1.15)	0.75 (0.54–1.05)
Stroke, HR (95% CI)	0.86 (0.71–1.06)	0.61 (0.38–0.99)‡	0.81 (0.76–0.94)	0.74 (0.47–1.17)
Secondary composite renal outcome, HR (95% CI)	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.85 (0.77–0.93)	0.77 (0.57–1.02)

†Primary outcome in all trials was a composite of CV death, non-fatal MI and non-fatal stroke.
‡Includes non-fatal events only.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes.

countered by a 2% increase in the absolute risk of significant adverse events.[48]

Inhibition of the renin–angiotensin system (RAS) is a key element in preventing microvascular complications. It is regarded as the first pillar in a multifactorial approach to preventing the progression of diabetic nephropathy, well summarised in a recent review by Naaman and Bakris.[30] In the UKPDS cohort, a 10% risk reduction in microvascular endpoints was seen for every 10mmHg decrement in blood pressure (to a target of <130 mmHg) achieved through antihypertensive therapy with captopril or atenolol.[21] Key evidence in T1D comes from the EUCLID study, which demonstrated a significant reduction in albuminuria over 2 years of follow-up in individuals randomised to lisinopril.[49] Similar benefits were seen in people with T2D in the MICRO-HOPE study using ramipril and the RENAAL study using losartan.[50,51]

Focussing on retinopathy in T1D and T2D, a Cochrane review of 15 RCTs found that intensive blood pressure control was associated with a relative risk reduction of 22% with respect to a combined outcome of incidence and progression.[52] Another meta-analysis examining the effects of specific antihypertensive classes found that the risk of retinopathy progression was lowest for ACE inhibitors, followed by angiotensin receptor blockers (ARBs), beta-blockers and calcium channel blockers (CCBs).[53]

International guidelines generally recommend a target blood pressure of <130/80 mmHg if this can be safely achieved. ACE inhibitors or ARBs are recommended as first-line agents, especially in patients with established albuminuria or cardiovascular disease, with the addition of CCBs or thiazide diuretics as second- and third-line strategies.[54]

Lipids

Lipid-lowering therapy is another cornerstone of cardiovascular risk reduction. The CARDS trial, which enrolled adults with T2D with normal or mildly elevated lipids, and without a history of cardiovascular disease, was stopped 2 years early after demonstrating a 37% reduction in the composite endpoint of MI, coronary revascularisation or stroke in the group assigned to low-dose atorvastatin.[55] The ASPEN trial, which similarly enrolled subjects with T2D and within-target low-density lipoprotein cholesterol levels, demonstrated only non-significant benefits of low-dose atorvastatin on a variety of cardiovascular outcomes.[56] A subsequent meta-analysis of statin use in people with T2D showed a 9% reduction in all-cause mortality, as well as significant reductions in the rate of cardiovascular mortality, MI, coronary revascularisation and stroke. These benefits were similar irrespective of baseline characteristics, including a prior history of cardiovascular disease.[57] RCTs assessing the use of fenofibrate in people with T2D, either as an add-on to statin therapy (ACCORD) or without statins (FIELD), did not demonstrate significant cardiovascular benefits.[58,59]

Suggested lipid targets for primary and secondary prevention of cardiovascular disease in T2D are summarised in Table 5. Moderate-intensity statins are the preferred first-line therapy in addition to lifestyle measures for people with diabetes and dyslipidaemia for primary prevention, whereas high-intensity statins are recommended for all people with diabetes and established atherosclerotic disease. For both primary and secondary prevention, ezetimibe and PCSK9 inhibitors can be added if lipid targets cannot be reached with maximally tolerated statin therapy.[54] Although recommendations for lipid-lowering treatment are generally extrapolated from trials in T2D, it is reasonable to initiate statins in younger adults with T1D and dyslipidaemia when other cardiovascular risk factors are present, such as obesity, hypertension or smoking.[60]

The role of lipid-lowering therapy in preventing microvascular complications is less clear than for macrovascular disease. In the CARDS trial, atorvastatin was associated with modest improvements in eGFR in people with T2D, particularly in participants with established albuminuria, though there was no significant effect on the incidence or progression of albuminuria.[61] A subsequent meta-analysis of 14 RCTs showed the

Table 5 Recommended lipid targets for primary and secondary prevention of cardiovascular disease in people with diabetes

	Patient selection	Treatment targets
Primary prevention	Consider treatment if age <40 and additional risk factors present Treatment recommended if age 40–75, especially if additional risk factors present	LDL reduction of ≥50% from baseline and target <1.8 mmol/L
Secondary prevention	Treatment recommended at all ages	LDL reduction of ≥50% from baseline and target <1.4 mmol/L

LDL, low-density lipoprotein.

benefits of statin therapy in albuminuria over 3 years, with a greater reduction in patients with existing diabetic nephropathy, but no significant effects were seen on eGFR.[62] There is limited evidence for specific benefits of statin therapy in either retinopathy or neuropathy.[63,64]

Fenofibrate has demonstrated benefits in retinal outcomes that appear to be independent of its lipid-lowering effects. In the FIELD study, a 31% reduction was seen in the risk of progression of retinopathy or need for laser therapy in patients randomised to receive fenofibrate.[59] A meta-analysis of three RCTs found a non-significant benefit of fenofibrate on the need for laser treatment in the first year of therapy, but after the first year there was a significant 30% reduction, suggesting that benefit accrues with time.[65] In another meta-analysis, fibrate therapy was associated with a 45% reduction in the risk of incident retinopathy, although no benefits were observed with respect to the progression of existing retinopathy.[63]

Aspirin

Low-dose aspirin, previously recommended in guidelines for the primary prevention of cardiovascular disease in people with T2D, is no longer standard. The ASCEND trial, which randomised adults with T2D and no history of cardiovascular disease to either aspirin or placebo, found a 12% reduction in cardiovascular events in the intervention group but a 29% increase in the rate of major bleeding events.[66] Aspirin is still strongly recommended for secondary prevention in any patients with previous MI or stroke.[54]

Finerenone

The selective mineralocorticoid receptor antagonist finerenone has been a recent agent of interest in the secondary prevention of diabetic nephropathy. In the FIDELIO-DKD trial, patients with T2D and CKD who received finerenone had a 28% reduction in the relative risk of progressive renal impairment as well as a 14% relative risk reduction in the secondary outcome of major adverse cardiovascular events.[67] The international KDIGO guidelines suggest the addition of finerenone in patients with persistent albuminuria despite maximally tolerated RAS blockade and SGLT2 inhibition, as long as serum potassium is not elevated.[68] Finerenone is currently approved in T2D only; the FINE-ONE trial will assess its effect in people with T1D and albuminuric nephropathy.[69]

Non-alcoholic fatty liver disease

There is increasing recognition of non-alcoholic fatty liver disease (NAFLD) as a common and important complication of diabetes. NAFLD encompasses a spectrum of diseases ranging from non-alcoholic fatty liver without inflammation, to non-alcoholic steatohepatitis (NASH), to cirrhosis. Recent studies have estimated that NAFLD occurs in over 70% of people with T2D and over 20% of

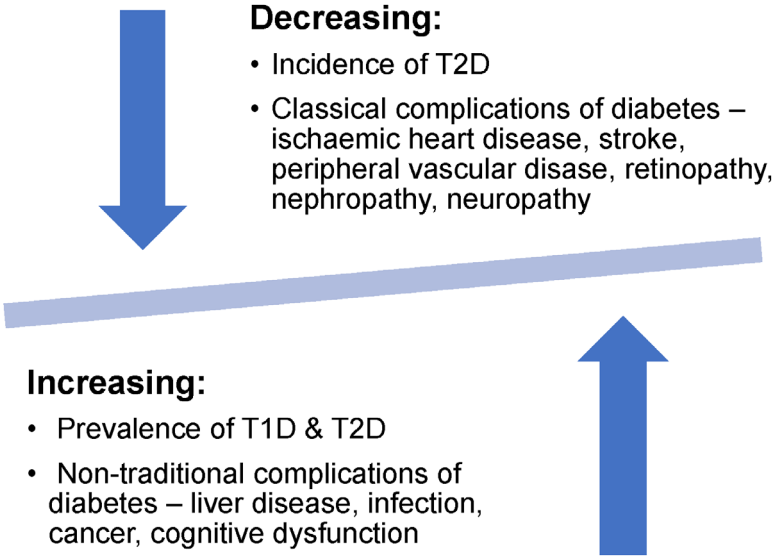

Figure 2 Summary of trends in diabetes epidemiology in recent decades. T1D, type 1 diabetes; T2D, type 2 diabetes.

people with T1D.[70] Strategies to prevent the onset of NAFLD are not yet clear; rather, the key strategy currently is screening for NAFLD to identify patients at risk of cirrhosis and hepatocellular carcinoma and to prevent progression of fibrosis. Screening strategies are summarised in recent ADA guidelines and include an initial non-invasive fibrosis-4 index (FIB-4) score followed by transient elastography or a serum-enhanced liver fibrosis test.[70] The cornerstone of improving fibrosis in people with NAFLD is lifestyle change, with a particular focus on weight loss. The efficacy of newer therapies in NAFLD remains under investigation, but GLP-1 receptors in particular may be beneficial: in a RCT of patients with NASH (62% with T2D), histologic resolution of NASH was seen in 59% of participants receiving higher-dose semaglutide compared with 17% in the placebo group.[71]

Emerging complications

Large reductions over time in the classic macro- and microvascular complications of diabetes have been accompanied by a growing awareness of non-traditional or 'emerging' complications of diabetes.[72,73] The reduction in the rates of – and mortality from – classic diabetes complications has led to longer life expectancies for people with diabetes[74] and recognition of a new suite of complications that are not necessarily preventable through the traditional risk reduction means of improving glucose, blood pressure and lipids. Figure 2 demonstrates the epidemiological trends in the incidence, prevalence and complications of diabetes over recent decades.

Some of the non-traditional complications of diabetes include infection, cognitive dysfunction and cancers, particularly those of the gastrointestinal system.[72] While the link between poorer glycaemic control and risk of infection in people with T2D has been established,[75] no association has been observed between glycaemic control and the risk of cancer or cognitive impairment.[76,77] Tomic *et al*. suggest that the current clinical approach to diabetes management may focus too narrowly on the prevention of vascular complications, and they call for a more holistic approach.[72]

Conclusion

The burden of managing diabetes complications is significant to both individuals and healthcare systems. Although rates of complications are declining on an individual level, the increasing rates at a population level because of rising prevalence of diabetes means the imperative is greater than ever to prevent their development and progression. Evidence has shown that a multifactorial approach is essential, focussing not only on glycaemia but also on lifestyle and control of blood pressure and lipids. Newer glucose-lowering agents – SGLT2 inhibitors and GLP-1 agonists – should be considered in every patient with T2D for their cardiorenal benefits. There is also growing recognition of non-traditional complications of diabetes that may not respond to traditional risk factor modifications and may require an expansion of the current approach to diabetes management.

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