Reducing cardiovascular risk in patients with type 2 diabetes mellitus

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Abstract

As obesity rates and life expectancies increase, diabetes mellitus continues to become more prevalent worldwide. Its complex pathophysiology is associated with micro- and macrovascular complications, with cardiovascular disease the leading cause of death in individuals with diabetes. Traditional anti-hyperglycaemic drugs have helped to improve glycaemic control without reducing cardiovascular complications, but novel agents such as sodium-glucose cotransporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists have shown an effective reduction of adverse cardiovascular events. The management of diabetes focuses on reducing low-density lipoprotein-cholesterol, lowering blood pressure and keeping glycated haemoglobin within recommended limits. Pharmacological and lifestyle interventions should address all potential risk factors to improve cardiovascular outcomes in patients with diabetes.

Keywords Antihypertensive; cardiovascular; diabetes; glucagon-like peptide-1 (GLP-1); HbA_{1c}; MRCP; sodium-glucose cotransporter-2 (SGLT-2); statins

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. The causes are multifactorial and include rising rates of obesity, longer life expectancy and improved screening programmes. T2DM is associated with increased cardiovascular complications and mortality, with a trebling of risk of developing coronary artery disease (CAD) and a 2-fold increase in risk of an acute coronary syndrome. After an initial cardiovascular event, even on optimal therapy, there is an additional doubling of coronary risk. Traditional anti-hyperglycaemic agents have failed to reduce cardiovascular complications, although early control of blood glucose concentrations has shown long-term cardiovascular benefit.

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Key points

- Prevalence of diabetes is increasing worldwide
- Coronary artery disease is the leading cause of death in diabetes patients
- Type 2 diabetes mellitus (T2DM) is a complex and heterogeneous condition
- Management of T2DM aims to prevent complications, allowing improved quality of life
- Novel agents such as glucagon-like peptide (GLP)-1 receptor agonists and sodium-glucose cotransporter (SGLT)-2 inhibitors improve glycaemic control without causing weight gain and hypoglycaemia
- SGLT-2 inhibitors and GLP-1 receptor agonists are the first agents to demonstrate significant reduction in cardiovascular morbidity and mortality in patients with T2DM

The treatment landscape for reducing cardiovascular complications in patients with diabetes has improved with newer generation of drugs. In particular, sodium-glucose cotransporter (SGLT)-2 inhibitors and glucagon-like peptide (GLP)-1 receptor agonist use have shown significant reductions in cardiovascular disease and overall mortality. Both drug classes have a low risk of hypoglycaemia and induce weight loss, in addition to targeting various vascular pathological pathways. Recent large-scale clinical trials have confirmed cardiovascular benefits, with mortality reduction in patients with cardiovascular disease. Consequently, these agents should be considered earlier in management of individuals with diabetes in the presence of existing cardiovascular disease.[1]

The goal of strategies to manage diabetes is to reduce mortality and morbidity related to the microvascular and macrovascular complications. This involves a multifactorial approach, aiming to stabilize both blood pressure and lipid concentrations, and improve lifestyle, to reduce the risk of cardiovascular disease (Figure 1). This article focuses on exploring the effects of anti-hyperglycaemic agents on cardiovascular disease.[1]

Epidemiology of diabetes mellitus and cardiovascular disease

A total of 387 million people, 8.3% of adults worldwide, have T2DM. In 2014, 4.9 million people died from complications of diabetes, and it is estimated that, in the next 20 years, 1 in 10 adults will have T2DM. Patients with T2DM have a 1.76-fold increased risk of death from cardiovascular disease, and a 2.26-fold increased risk of stroke.[1]

A significant proportion of diabetic patients have pre-existing cardiovascular disease at the time of diagnosis, and over half die from a cardiovascular complication.[2] These patients have a worse prognosis than cardiovascular disease patients who do not have diabetes.[3]

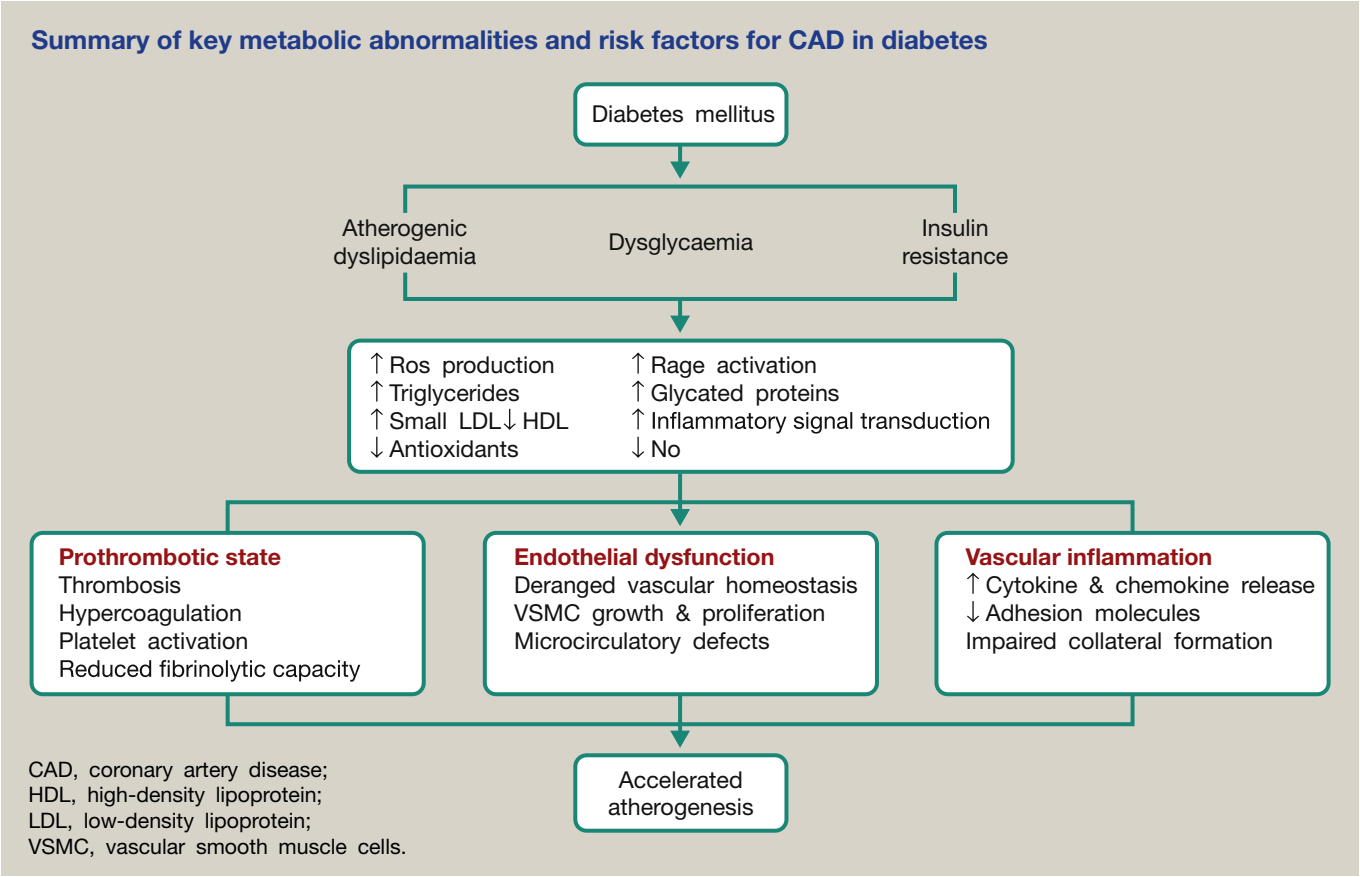

Figure 1

Lifestyle modification

The American Diabetes Association (ADA) guidelines advise medical nutrition therapy (MNT) and physical activity for initial management of diabetes. The goals of MNT are to improve eating patterns, to achieve and maintain weight, glycaemic control, blood pressure and lipid profile. Exercise programmes should include regular exercise $\geq$ 3 days/week, resistance training $\geq$2 times/week and to reduce sedentary time.[4]

Pharmacological therapies to prevent cardiovascular complications in people with T2DM

Control of low-density lipoprotein cholesterol (LDL-C) concentrations and blood pressure to guideline recommended levels are essential to improving cardiovascular status in T2DM patients are core to standard care for T2DM patients.[5]

Lipid management

The main goals in the management of T2DM are to achieve target concentrations of LDL-C (<2.0 mmol/litre), serum triglyceride (triacylglycerol; <1.7 mmol/litre) and high-density lipoprotein-cholesterol (HDL-C) (>1.0 mmol/litre). Many systematic reviews have highlighted that patients with or without T2DM have similar benefits from the use of statins. However, statins have little or no effect on HDL-cholesterol (see Further reading).

LDL-C is the primary target of lipid-lowering therapy in diabetic patients. Trials have demonstrated significant advantage of statin therapy, for cardiovascular disease prevention, in patients with diabetes. Meta-analyses support the use of early, intensive and long-term statin therapy in patients who have cardiovascular disease. Patients who have recently suffered from acute coronary syndrome (ACS) are recommended to be started on high dose statin therapy for at least 4 days of hospitalization. High-dose statin therapy also decreased peri-procedural myocardial infarction (MI) and 30-day adverse events in patients undergoing percutaneous coronary intervention (PCI) (see European Society of Cardiology, Further reading).

Ezetimibe can be offered to patients with heterozygous familial hypercholesterolaemia or non-familial hypercholesterolaemia as a monotherapy when, statins are a contraindication or not tolerant and in those patients in which serum total or LDL-C concentrations are not appropriately controlled.

PCSK-9 inhibitors are given in patients with primary hypercholesterolaemia and mixed dyslipidaemias when, LDL-C concentrations are persistently above the threshold despite receiving maximum tolerated lipid-lowering therapy.

The NICE guidelines recommend that adults with familial hypercholesterolaemia and intolerance or contraindications to statins or ezetimibe should be considered for treatment with fibrates, bile acid sequestrant or nicotinic acid to reduce LDL-C concentration. However, in type 1 diabetes, type 2 diabetes and chronic kidney disease fibrates should not be given as a monotherapy (see Further reading).

Antihypertensives

Treatment with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; if the individual is intolerant of ACEs) decreases the progression of albuminuria, promotes normoalbuminuria and may eventually reduce the risk of renal dysfunction. The target blood pressure should be <140/90 mmHg, and in patients with renal dysfunction <130/80 mmHg.[5]

Other alternative antihypertensives include calcium channel blockers and diuretics; usually a thiazide diuretic can be used. If blood pressure does not respond to the three mentioned drug classes, then an α-blocker, β-blocker or a potassium-sparing diuretic can be added, though with caution.

Intensive glycaemic control

The UK Prospective Diabetes Study (UKPDS) 33 assessed effectiveness of intensive glycaemic control in comparison to conventional therapy in patients who were newly diagnosed or had a short duration of diagnosed diabetes. Over 10 years of intensive glycaemic control and conventional therapy, median glycated haemoglobin (HBA_{1c}) concentrations of 53 and 63 mmol/mol (7.0% and 7.9%), respectively, were achieved. There was no statistical difference in macrovascular complications when comparing the two study arms, although the difference just failed to reach statistical significance ($p = 0.052$). However, there were fewer microvascular complications, such as retinopathy and renal failure, in intensive glycaemic control arm.

Longer follow-up of these patients showed a reduction in vascular events in patients enrolled on the intensive arm of the study, raising the question of a 'legacy effect' – meaning that targeting glycaemic control early resulted in fewer long-term cardiovascular complications (Table 1).[1]

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, conducted on patients with type 1 diabetes and with extended follow-up, showed similar findings, further emphasizing the importance of early glycaemic control for reducing long-term vascular events (see Table 2).

Existing antihyperglycaemic agents

Metformin

In the UKPDS 34 trial, metformin was found to reduce the risk of myocardial infarction (39%), coronary deaths (50%) and all-cause mortality (36%), in comparison to conventional therapy. A 10-year follow-up of this trial continued to show reductions in myocardial infarctions and all-cause mortality. These findings are, however, tempered by the small sample size (342 patients) and the inclusion of overweight individuals. The mechanisms of action are not completely understood, but suggestions for the improved outcomes include improving lipid profiles, antiatherogenic effects, reduced ischaemic injury and amelioration of oxidative stress.[1]

Sulfonylureas

Sulfonylureas have not been shown to reduce cardiovascular risk. In fact, they increase the risk of hypoglycaemia and weight gain, which may indirectly increase the risk of cardiovascular disease. A meta-analysis of trials involving the cardiovascular effectiveness of sulfonylureas concluded, however, that the overall risk of major cardiovascular events was not increased by this agent in comparison to others (see Monami M, et al., Further reading).

Cardiovascular changes affecting diabetes

Risk factor	Effect
Dyslipidaemia	Increased LDL and triglyceride-rich VLDL Reduced HDL
Endothelial dysfunction	Increased expression of cellular adhesion molecules Impaired vasomotor activity due to decreased availability of nitric oxide
Oxidative stress	Increased concentrations of markers such as oxidized LDLs and F2-isoprostanes
Inflammation	Increased expression of markers such as fibrinogen and CRP
Abnormalities of coagulation and fibrinolysis	Overproduction of fibrinogen Increased production of PAI-1
Glycation of proteins	Formation of proatherogenic advanced glycation end products (AGE) in LDL and collagen within the arterial wall

CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor -1; VLDL: very low-density lipoprotein.
Adapted from Kapur, A and Qureshi, A. (2010) Oxford textbook of interventional cardiology. City; Oxford University Press; 2010.

Table 1

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor-γ agonists. They can increase body weight and risk of congestive heart failure. A meta-analysis of rosiglitazone and pioglitazone established that, despite being in the same class, they have differing cardiovascular adverse effects. Rosiglitazone is either neutral or associated with increased vascular risk, whereas pioglitazone seems to offer protection from cardiovascular events.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Some studies have reported cardiovascular effects of DPP-4 inhibitors including improved endothelium-dependent vasodilation, reduction of atherosclerotic lesions and improvements in left ventricular function after a myocardial infarction. Overall, current evidence suggests that these agents are safe in patients with cardiovascular disease, but no significant cardiovascular benefit in comparison to placebo was shown.[1]

Antihyperglycaemic agents with vascular protective properties

SGLT-2 inhibitors

Potential cardiovascular risk factors that can be modulated by SGLT-2 inhibitors include blood pressure, weight, visceral adiposity, hyperinsulinaemia, arterial stiffness, cardiorenal

Diagnostic criteria for diabetes mellitus

- HbA_{1c} measurement is now the recommended diagnostic test for diabetes mellitus (World Health Organization, 2010)
- HbA_{1c} ≥48 mmol/mol (≥6.5%) on *two* occasions is diagnostic of diabetes. (You should not make a diagnosis of diabetes if *either* reading is <48 mmol/mol (6.5%))
- HbA_{1c} of 42–47 mmol/mol (6.0–6.5%) is associated with a high risk of developing diabetes, so patients should be offered intensive modification of risk factors and annual HbA_{1c} testing
- HbA_{1c} <42 mmol/mol (<6.0%) may still carry a high risk of diabetes, so patients should be treated according to clinical indications, with retesting at least every 3 years
- Glucose testing should still be used in conditions where HbA_{1c} is an unreliable diagnostic marker of diabetes mellitus, such as:
  - All children and young people
  - Pregnancy
  - Type 1 diabetes
  - Haemoglobinopathies
  - Short duration of symptoms, or suspected new onset in people starting drugs (e.g. corticosteroids, antipsychotics) that may have precipitated diabetes within the last 2 months
  - Acute illness (HbA_{1c} <48 mmol/mol (<6.5%) does not exclude diabetes)
  - Acute pancreatic damage or surgery
  - Renal failure
  - HIV infection

Source: World Health Organisation (WHO). Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation 2011.

Table 2

effects, cardiac oxygen demand, cardiac function and lipid concentrations.

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) involved 7020 T2DM patients with an average age of 63 years. All participants had established cardiovascular disease, and were randomly assigned different doses of empagliflozin or placebo in addition to their standard diabetic therapy. Patients randomized to empagliflozin recorded a 38% reduction in cardiovascular mortality and a 32% reduction in all-cause mortality. There was a 35% reduction in hospitalization for heart failure, alongside improvements in renal function. Other benefits were a decrease of 8 mmol/mol (0.6%) in HbA_{1c}, a 2.5 kg weight reduction and a 5.2 mmHg fall in systolic blood pressure.

Qualitatively similar findings were seen in the Canagliflozin Cardiovascular Assessment Study (CANVAS) programme, involving 10,142 participants with T2DM and high risk of cardiovascular disease. The rates of myocardial infarction, stroke and cardiovascular-related mortality were lower in participants given canagliflozin compared with placebo. (see Zinman B, et al., Further reading).

GLP-1 receptor agonists

Cardiovascular outcome trials have evaluated the safety of exenatide, liraglutide and lixisenatide and revealed no adverse effect of these drugs on cardiovascular outcomes. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER) trial observed the effects of liraglutide when added to standard treatment for T2DM. The 9340 participants in this study were randomly assignment liraglutide (0.6–1.8 mg/day) or placebo. The primary outcome of myocardial infarction, stroke and death from cardiovascular cause was significantly lower in the group given liraglutide.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) involved 14,752 participants with T2DM, with or without cardiovascular disease. The risk of myocardial infarction, non-fatal stoke and cardiovascular-related death was lower, at 11.4%, in participants given exenatide in comparison to those given placebo (12.2%), but narrowly missed statistical significance ($p = 0.061$).[1]

Treatment strategy

Patients with diabetes mellitus are at increased risk of cardiovascular complications, so control of known risk factors is paramount. The goal of managing T2DM is to reduce morbidity and mortality and improve quality of life. Statins remain the drug of choice when starting therapy to reduce LDL-cholesterol concentrations. ACE inhibitors (or ARBs if the patient is intolerant) are used to maintain a systolic blood pressure <140 mmHg, or <130 mmHg in the presence of renal impairment. For each patient, individualized targets are set for maintaining HbA_{1c} concentration.

The recent introduction of novel pharmacological agents with cardiovascular benefits has led to a reappraisal of drug choices made to manage T2DM and its cardiovascular complications. SGLT-2 inhibitors and GLP-1 receptor agonists lower blood glucose without increasing the risk of hypoglycaemia, and can be used to reduce cardiovascular risks, as shown in the trials mentioned above. As T2DM is a complex chronic condition, each individual patient and their risk factors must be taken into consideration, rather than prescribing generically. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old man presented with a 4-month history of polyuria and polydipsia. He had gained about 6 kg in weight in the previous 6 months, related to retiring from work. Test strip (BM) showed random blood glucose of 15 mmol/litre (3.0–6.0) on one occasion.

Investigation

- LDL-cholesterol 5.2 mmol/litre (<3.36)
- HbA_{1c} 56 mmol/mol (20–42); 7.8% (4.0–6.0) on two occasions

Which feature in this patient confirms a diagnosis of diabetes according to the latest World Health Organization advice?

A Hba_{1c} >48 mmol/mol (>6.5%) on two different occasions
B Random BM >11 mmol/litre on one occasion
C Fasting BM >7 mmol/litre on one occasion
D Symptoms of diabetes for >3 months
E Weight gain of 5 kg and LDL-cholesterol >4 mmol/litre

Question 2

A 60-year-old man had been found to have type 2 diabetes. His 24-hour blood pressure monitoring and random blood pressure checks all displayed a systolic blood pressure >150 mmHg. His heart rate had been noted to be between 60 and 75 beats/minute, and in sinus rhythm.

Which of the following medications should he be advised to take to manage his hypertension?

A Amlodipine
B Ramipril
C Losartan
D Canagliflozin
E Bisoprolol

Question 3

A 55-year-old woman presented for review 3 months after a non-ST elevation myocardial infarction. At the review, she was found to have type 2 diabetes.
On clinical examination, her blood pressure was 145/90 mmHg, and body mass index 32 kg/m^2.

What anti-hyperglycaemic agent would she be best advised to take?

A Gliclazide
B Pioglitazone
C Empagliflozin
D Insulin glargine
E Saxagliptin