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REVIEW

Clinical update

Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II

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In part II of this review, we describe the epidemiology and clinical consequences of vascular disease in patients with diabetes, and discuss the efficacy of risk factor modification and antiplatelet treatment. Specifically, evidence-based cardiovascular therapies are discussed through novel clinical insights on management of hyperglycaemia, hypertension, dyslipidaemia as well as platelet dysfunction. Recent trends in the incidence and outcomes of vascular disease in diabetes suggest that timely and effective implementation of therapies is making a favourable impact.

Keywords Diabetes • Vascular disease • Medical therapy

Introduction

Diabetes and vascular disease are intimately linked and share pathophysiological features as examined in Part I of this review. In this section, we review the epidemiology and clinical consequences of vascular disease in patients with diabetes, and discuss the efficacy of risk factor modification and antiplatelet treatment. Since the reviews published on this topic by the authors previously,[1,2] contemporary trends in the incidence and outcomes of vascular disease in diabetes suggest that timely and effective implementation of therapies is making a favourable impact.

Epidemiology of diabetes and atherosclerosis

In the late 1990's and early 2000s, there was a marked increase in the rate of obesity and diabetes across the globe.[3] These changes were observed and reported in the United States,[4] Europe,[5,6] Africa,[7] China,[8,9] and India.[10] In 1997, Amos *et al.*[11] predicted the worldwide burden of diabetes would increase from 124 to 221 million people in 2010, with particular gains in Asia and Africa. In retrospect, these predictions now seem optimistic as the World Health Organization estimates a current worldwide prevalence of 346 million patients with diabetes[12] (*Figure 1*). Evidence suggests that the rates of obesity and diabetes may be leveling off in Europe and the United States but continue to increase in Asia and Africa, making clear the global nature of the problem.[13–16]

Recently, investigators have identified subsets of patients with diabetes at the highest risk. In a meta-analysis of 29 clinical trials that included at least 1000 patients with diabetes, two factors were noted to identify a higher risk cohort within the diabetes population: the presence of cardiovascular disease and the presence of proteinuria.[17] Cardiovascular disease increased the rate of all-cause death nearly three-fold and the rate of cardiovascular death nearly five-fold in subjects with diabetes. These results are in concordance with another systematic review of large trials in patients with diabetes, demonstrating the association of renal disease, measured either by the function or presence of proteinuria with increased mortality.[18]

Coronary heart disease

The impact of diabetes on atherosclerosis is best documented in terms of its association with coronary heart disease and cardiovascular events. Several studies make clear that patients with diabetes are several-fold more likely to develop myocardial infarction than matched subjects without diabetes. In a seminal Finnish study, the presence of diabetes increased the 7-year risk of myocardial infarction and death in older subjects.[19] It was from this study that the concept of diabetes as a coronary heart disease risk-equivalent began, and culminated in its coronation as a high-risk cardiovascular state requiring secondary prevention level care as recommended in

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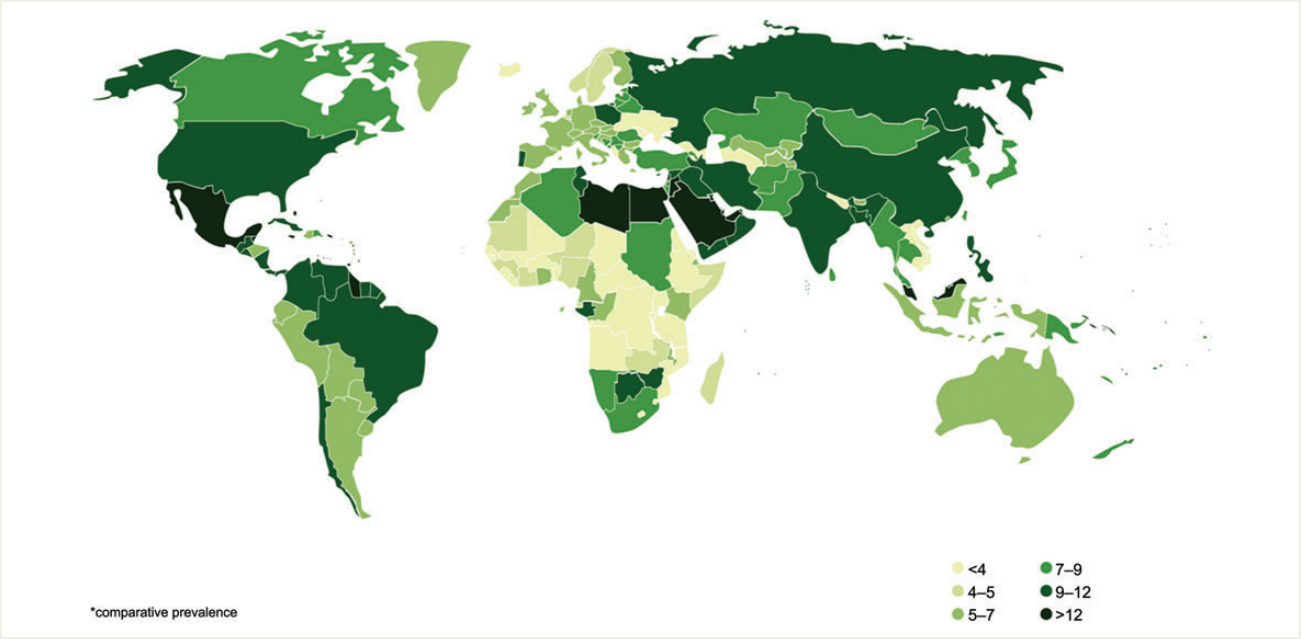

Figure 1 Worldwide prevalence of diabetes mellitus in persons aged 20–79 years. The prevalence of diabetes is high. Colours indicate percent prevalence in respective nations. *Source*: Diabetes Atlas 5, International Diabetes Federation. Permission granted by the International Diabetes Federation.

the Adult Treatment Panel III of the National Cholesterol Education Program several years later.[20] More recent evidence, however, suggests that although diabetes increases the risk of coronary heart disease, it may not reach risk-equivalence for adverse cardiovascular outcomes. In a Danish population study, the risk of adverse cardiovascular events (composite of myocardial infarction, stroke, or cardiovascular death) was lower in both men and women with diabetes and no prior myocardial infarction than in non-diabetic men and women with prior myocardial infarction.[21] Bulugahapitiya *et al.*[22] reviewed 13 studies, comprising 45 108 patients with follow-up ranging from 5 to 25 years. In this meta-analysis, patients with diabetes had a 43% lower risk of developing coronary heart disease events than patients without diabetes but with previous myocardial infarction. The lesser cardiovascular risk found in the meta-analysis as compared with previous studies, may be attributed, in part, to the lower glucose threshold used for the diagnosis of diabetes, such that a relatively less sick population now carried the same diagnosis.[23] Nonetheless, patients with diabetes still carry a significantly increased risk of coronary heart disease compared with patients without it.

Despite the lack of risk equivalency, the relevance of diabetes to atherosclerosis has been made clear through another observation: a majority of patients with coronary heart disease have insulin resistance or frank diabetes. Norhammar *et al.*[24] studied 181 consecutive patients admitted to coronary care units with acute myocardial infarction and glucose of <11.1 mmol/L. Despite specifically excluding subjects with known diabetes, oral glucose tolerance testing (OGTT) at discharge showed that 35% of subjects had impaired glucose tolerance and 31% had previously undiagnosed diabetes. These results were confirmed in the much larger Euro Heart Survey performed in 110 medical centres in 25 nations.[25] In Euro Heart, 4961 subjects with coronary artery disease but no known diabetes were enrolled,

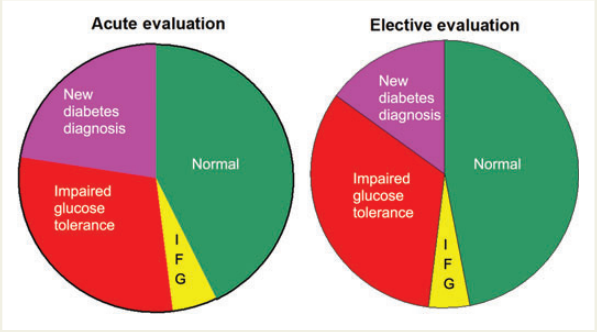

Figure 2 Insulin resistance in patients referred for cardiac evaluation. Results of oral glucose tolerance testing in a survey of 4196 non-diabetic patients referred to a cardiologist for coronary artery disease (2107 for an acute cardiac problem and 2854 for an elective evaluation) from 110 centres in 25 countries. More than half of all patients with coronary artery disease, when presenting with an acute or chronic cardiac condition, have evidence of insulin resistance, even after excluding patients with known diabetes. IGT, Impaired glucose tolerance. Adapted from Bartnik *et al.*[25]

and a majority of these patients were subsequently found to have diabetes, impaired glucose tolerance, or impaired fasting glucose (*Figure 2*). Using OGTT, 18% of subjects were newly diagnosed with diabetes, 32% had impaired glucose tolerance, and 5% had impaired fasting glucose. The results have been replicated in non-European populations as well.[26]

Even in recent clinical trials, adverse events associated with symptomatic coronary heart disease are higher in patients with diabetes

than in patients without it. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes[6]-TIMI 36 trial of 6560 patients with non-ST-segment elevation myocardial infarction, subjects with diabetes had higher rates of the composite endpoint of cardiovascular death, myocardial infarction, or recurrent ischaemia.[27] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38),[28] of 13 608 subjects with acute coronary syndromes, prasugrel lowered adverse event rates, but patients with diabetes still had higher levels of myocardial infarction, cardiovascular death, and stent thrombosis than patients without diabetes. In a Danish study of 3655 consecutive patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention, diabetes was associated with a more than two-fold increase in the rate of myocardial infarction and all-cause mortality over 3 years of follow-up.[29] Diabetes worsens outcomes after coronary revascularization as well, with higher rates of stent thrombosis, both early and late,[30–33] and mortality after coronary artery bypass grafting.[34,35] In a prospective cohort study of more than 36 000 patients, those with diabetes had a 25% excess mortality compared with those without.[36] Complications of diabetes, like renal failure, further increase the rate of adverse events when compared with diabetes alone.

Over the last decade, both the recognition by the medical community of the impact of diabetes on atherosclerosis and the efforts to modify the increased risk have improved.[37] In Sweden, risk factor modification has improved in this cohort even years after diagnosis. Fhärm *et al.*[38] evaluated 19 382 diabetic patients in cross-sectional surveys from 2003 to 2008 as well as a subgroup of 4293 patients followed individually from the year of diagnosis to a mean 2.6 years of follow-up. They found that treatment goals for HbA1c, blood pressure, total cholesterol, and LDL cholesterol improved over the 5 years of cross-sectional analysis and were achieved ultimately in 78.4, 65.5, 55.6, and 61.0% of patients, respectively. The results were similar in the National Health and Nutrition Surveys (NHANES) over the 1998–2008 time period. Significant improvements were seen in the control of HbA1c (37.0–55.2%), blood pressure (35.2–51.0%), and low-density lipoprotein-cholesterol (LDL-C; 32.5–52.9%).[39]

As a result of better available medical therapy and more pervasive use of these therapies, the risk of myocardial infarction in the patients with diabetes has diminished. Using the United Kingdom Prospective Diabetes Study risk calculator, the estimated 10-year risk for coronary heart disease decreased from 21.1% in 1999–2000 to 16.4% in 2007–2008.[40] The impact of therapy may even extend to mortality. Gregg *et al.*[41] compared 3-year death rates of four consecutive nationally representative samples from the National Health Interview Surveys linked to National Death Index (1997–1998, 1999–2000, 2001–2002, and 2003–2004) of US adults aged 18 years and older. Among the individuals with diabetes, the cardiovascular death rate declined by 40% and all-cause mortality declined by 23% when comparing the earliest and latest time periods. Reductions in mortality, however, were not noted in the Framingham population when pre-1976 and pre-2001 time periods were compared.[42] The difference in findings may reflect the routine incorporation of statins into therapy of patients with diabetes after the Heart Protection Study[43] was released in 2002.

Stroke

Diabetes also contributes significantly and increasingly to the burden of stroke.[44,45] In the INTERSTROKE case–control study, performed in 22 nations, diabetes increased the rate of stroke by 35% when comparing the top to the bottom tertile, and was associated with 5% of the population attributable risk for stroke.[46] The Emerging Risk Factors Collaboration analysed 698 782 people from 102 prospective studies, finding that diabetes was associated with a 2.27-fold increase in the risk of ischaemic stroke and 56% excess rate of haemorrhagic stroke.[47] Following a stroke, diabetes attenuates cognitive recovery,[48] limits functional outcome,[49] and increases mortality.[50] Diabetes increases the risk of recurrent stroke as well. In the Life Long After Cerebral ischemia (LiLAC) cohort study, diabetes increased the risk of recurrent fatal and non-fatal stroke more than two-fold.[51]

Identification and implementation of effective therapies have begun to reduce the risk of stroke in diabetes. In Finland, both the population attributable risk of stroke and prognosis after stroke are decreasing over time in patients with diabetes.[52,53] Improvements in control of hypertension, dyslipidaemia, and treatment of diabetes have been demonstrated as well in the NHANES survey,[54] and are likely contributing to more favourable outcomes and a lower rate of recurrence. Data showing better outcome of stroke overall are not uniform, however.[45,55] For example, Harmsen *et al.*[55] reported a tripling in the incidence of diabetes in patients with stroke, but no change in stroke incidence and mortality in Gothenburg, Sweden between 1987 and 2006.

Peripheral artery disease

Increasing rates of diabetes also have implications for the prevalence and prognosis of peripheral artery disease. In the German Epidemiological Trial on Ankle Brachial Index (GETABI), which screened 6880 consecutive primary care patients aged 65 years or older, 1743 (25.3%) had diabetes.[56] In the entire cohort, the prevalence of PAD, defined by an abnormal ankle–brachial index, was 19.8% for men and 16.8% for women.[57] Compared with patients without diabetes, patients with diabetes had a higher prevalence of PAD, (26.3 vs. 15.3%) and intermittent claudication (5.1 vs. 2.1%).[56] The rate of PAD in patients with diabetes also increases with age, as it does in non-diabetic persons. In a multicentre cross-sectional study of patients older than 70 years with diabetes, 71% had PAD when detected by abnormal ankle–brachial index.[58]

Diabetes increases the incidence of critical limb ischaemia (CLI) four-fold in patients with peripheral artery disease (*Figure 3*).[59] Moreover, in diabetic patients with CLI, 50% will develop CLI in the contralateral limb within 5 years.[60] Also, results of revascularization, whether percutaneous or surgical, are worse in patients with diabetes, and there is a higher rate of cardiovascular morbidity associated with the procedure.[61]

It is not established whether aggressive risk factor modification decreases the risk of PAD in patients with type 2 diabetes. In 1533 patients with type 2 diabetes randomized to intensive risk factor control or standard therapy, there was no difference after 6 years in the prevalence of peripheral artery disease.[62] Despite this, most data suggest that the rate of complications, and specifically diabetes-related amputation, declined over the last decade.[63–65] Using the

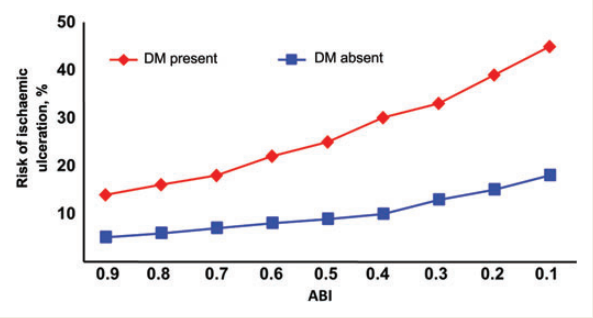

Figure 3 Incidence of ischaemic ulceration in a cohort of patient with intermittent claudication. A total of 1244 men with claudication were followed for a mean of 45 months. Over the follow-up period, men with diabetes were at a four-fold risk of ulceration for every level of reduction in ankle perfusion pressure compared with men without diabetes. DM, diabetes; ABI, ankle–brachial index. Adapted from Aquino *et al.*[59]

National Hospital Discharge Survey and National Health Interview Survey Data, Li *et al.*[66] showed a decrease in the age-adjusted non-traumatic lower extremity amputation rate per 1000 persons in patients with diabetes from 11.2 in 1996 to 3.9 in 2008. Despite this reduction, the rate of non-traumatic lower extremity amputation remains nearly eight-fold higher in patients with diabetes compared with those without it.

Treatment of atherosclerosis in diabetes

Advances in therapy have led to significant reductions in morbidity and mortality for patients with diabetes (*Table 1*). The primary focus of these treatments is the modification of risk factors for cardiovascular disease (*Figure 4*).

Hyperglycaemia

The potential role of glucose-lowering therapies in reducing cardiovascular events has been studied for more than two decades. Several factors suggest that elevated glucose levels would be an important therapeutic target. First, there is increased risk of cardiovascular events with the very earliest signs of increased glucose levels, even those below the threshold for a diagnosis of diabetes.[67] Early work with glucose-lowering therapies came tantalizingly close to demonstrating a reduction in cardiovascular events. In the United Kingdom Prospective Diabetes Study (UKPDS), there was a near statistically significant reduction in myocardial infarction[68,69] with tight glucose control. The close results prompted several other investigations to definitively answer the question. In The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study, 10 251 patients (mean age, 62.2 years) with a median glycosylated haemoglobin level of 8.1% were randomly assigned to intensive therapy [a haemoglobin (Hgb) A1c <6.0%] or standard therapy (a Hgb A1c of 7.0–7.9%).[70] Although there was a non-significant 10% trend in the reduction of the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), there was a significant 22% increase in all-cause mortality in the intensively treated group. A second large trial also failed to find any cardiovascular benefit to intensive control. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[71] 11 140 patients with type 2 diabetes were randomized to standard glucose control or intensive glucose control (Hgb A1c <6.5%). Intensive glucose control did not reduce major macrovascular events, death from cardiovascular causes, or death from any cause. A smaller, Veterans Affairs-based trial of more poorly controlled subjects with type 2 diabetes also demonstrated lack of efficacy with intensive control of hyperglycaemia.[72] A meta-analysis of 33 040 subjects from the five trials commonly associated with 'tight' vs. 'conventional' control of glucose showed a 17% reduction in myocardial infarction without improvement in stroke or all-cause mortality rates.[73] However, caution is required in the interpretation of these data: the intensive treatment goal of UKPDS was the same as the conventional goal of the more recent trials; the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), also included in this meta-analysis, compared the addition of a thiazolidinedione with placebo in patients with established atherosclerosis and was not specifically a study of more vs. less intensive therapy[74]; and the ACCORD actually showed a mortality hazard. As a result of these studies, the American Heart Association, American College of Cardiology, and American Diabetes Association concluded that a Hgb A1c goal of 7% should be maintained, and the decision to pursue tighter control could be made on an individual basis.[75]

In contrast to the failure of targeting a glucose level, targeting the mechanism of hyperglycaemia may yield better therapeutic outcomes. Improving insulin sensitivity, rather than insulin levels, is a strategy that has undergone study. The biguanide metformin has demonstrated efficacy when compared with insulinotropic sulfonylureas. In UKPDS, among subjects with >120% of ideal body weight, metformin was associated with a 42% reduction in diabetes-related death and 36% reduction in all-cause mortality.[68] The results were difficult to interpret, for in the same study the addition of metformin to a sulfonylurea was associated with an increase in mortality. In the 10-year follow-up of UKPDS, despite a lack of difference in glycosylated haemoglobin between the metformin and sulfonylurea arms in the 5 years after the initial study ended, metformin-treated patients had a 33% reduction in myocardial infarction and 27% reduction in death from any cause, both significantly more than that in the patients in the sulfonylurea arm.[76] The value of metformin has been supported in other studies as well. In the 19 691 diabetic patients with in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, those treated with metformin had a 24% reduction in mortality compared with those not treated with metformin.[77] In a nationwide Danish study, patients treated with an insulin secretagogue, suffered a 19–32% increase in all-cause mortality compared with those treated with metformin.[78] The results were similar whether or not the study subjects had a previous myocardial infarction. It is because of results like these that metformin is the recommended first hypoglycaemic agent to be used in patients with type 2 diabetes.[79] The thiazolidinediones, however, have a mixed record of success in terms of cardiovascular outcomes. In the (PROACTIVE) trial, pioglitazone missed its primary cardiovascular endpoint (composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, revascularization, and amputation) when

Table 1 Evidence for cardiovascular therapies in patients with diabetes mellitus

Condition	supporting literature
Hyperglycaemia	
In patients with diabetes	
The use of metformin to lower Hgb A1c to <7% in the prevention of cardiovascular disease events is likely of value.	UKPDS[76]
The use of hypoglycaemic medications to achieve a target Hgb A1c of 6–6.5% to reduce cardiovascular events is not beneficial and may be harmful when compared with a target of 7%.	ACCORD[70] ADVANCE[96]
Hypertension	
In patients with diabetes	
Blood pressure should be reduced to <140/90 mmHg in all risk settings.	ALLHAT[92]
Patients with CHD, CVD, or PAD should receive an antagonist of the renin–angiotensin system.	ALLHAT[92] HOPE[95] VALUE[104] ONTARGET[108]
Blood pressure should not be routinely lowered to a target of <120/80 mmHg.	ACCORD-Blood Pressure[91]
Acceptable initial agents in the treatment of uncomplicated hypertension include beta-adrenergic blockers, thiazide diuretics, and dihydropiridine calcium-channel blockers.	ALLHAT[92]
The use of alpha adrenergic blockers as initial therapy in uncomplicated hypertension is not recommended.	ALLHAT[92]
Dyslipidaemia	
In patients with diabetes	
All patients, with or without a history of atherosclerotic vascular disease, should be treated with statins.	HPS[43] CARDS[118]
Routine administration of fibrates or long-acting niacin in addition to therapy with statins is not useful.	ACCORD-Lipid[129] AIM-HIGH[131]
The use of fibrates may be effective in selected patients who manifest an HDL <34 mg/dL and triglycerides >204 mg/dL.	SACKS[130] FIELD[127]
Antiplatelet therapy	
In patients with diabetes	
The use of aspirin in the treatment of acute coronary syndromes and in the prevention of recurrent coronary syndromes has been established.	ISIS-2[141] AntiplateletTrialist's Collaboration[137]
The use of P2Y12 inhibitors in the treatment of acute coronary syndromes in addition to aspirin for the prevention of recurrent coronary syndromes is established.	CURE[145] TRITON[28]
P2Y12 inhibitors are superior to aspirin as monotherapy in patients with atherosclerotic vascular disease.	CAPRIE[142]
The value of aspirin in the primary prevention of atherosclerotic vascular disease is unclear.	JPAD[138] POPADAD[139]

compared with placebo, but showed benefit in its composite secondary endpoint (all-cause mortality, non-fatal MI, and stroke),[74] while rosiglitazone has been associated with an increase in myocardial infarction but not all-cause mortality.[80]

Several other hypoglycaemic medications are commonly employed for diabetes, but lack enough data to recommend their use as treatments to reduce cardiovascular events. Acarbose, an alpha glucosidase inhibitor, reduced the rate of myocardial infarction by 91% and a composite of cardiovascular events (myocardial infarction, new angina, revascularization, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) by 49% in subjects with impaired glucose tolerance in the STOP-Noninsulin Dependent Diabetes (NIDDM) trial.[81] However, cardiovascular risk reduction with acarbose has not been reported in patients with diabetes. Neither incretin mimetics, dipeptidyl peptidase (DPP)-4, nor sodium glucose co-transporter-2 (SGLT2) inhibitors have any clinical trial data demonstrating cardiovascular event reduction.

Ranolazine, a partial fatty acid oxidation inhibitor, improves functional capacity in patients with stable angina and has been shown to improve exercise tolerance similarly in patients with and without diabetes[82] but does not reduce cardiovascular outcomes.[27] As a partial fatty acid oxidation inhibitor, it improves glucose utilization and has consistently performed as a hypoglycaemic agent.[82,83] Despite the glucose-lowering capability, patients with diabetes do not gain extra function or improved cardiovascular outcomes with ranolazine. Current guidelines do not support the use of these agents to improve cardiovascular outcomes in patients with diabetes.[79] Moreover, the safety requirements for the approval of hypoglycaemic agents for type 2 diabetes has undergone scrutiny and now faces a higher threshold at the Food and Drug Administration in the United States.[84]

Hypertension

Treatment of hypertension was the first among the therapies of the comorbidities of patients with diabetes to reduce mortality. In UKPDS, 1148 hypertensive patients with diabetes were randomly allocated to tight (more intensive) or standard blood pressure control.[85] Followed for 8.4 years, patients in the tight control arm had a significantly lower blood pressure (144/82 mmHg) compared with those in the standard control arm (154/87 mmHg) and had a 44% reduction in stroke and a 32% reduction in diabetes-related death. The choice of first agent, beta-adrenergic blocker or angiotensin-converting enzyme inhibitor, made no difference in the

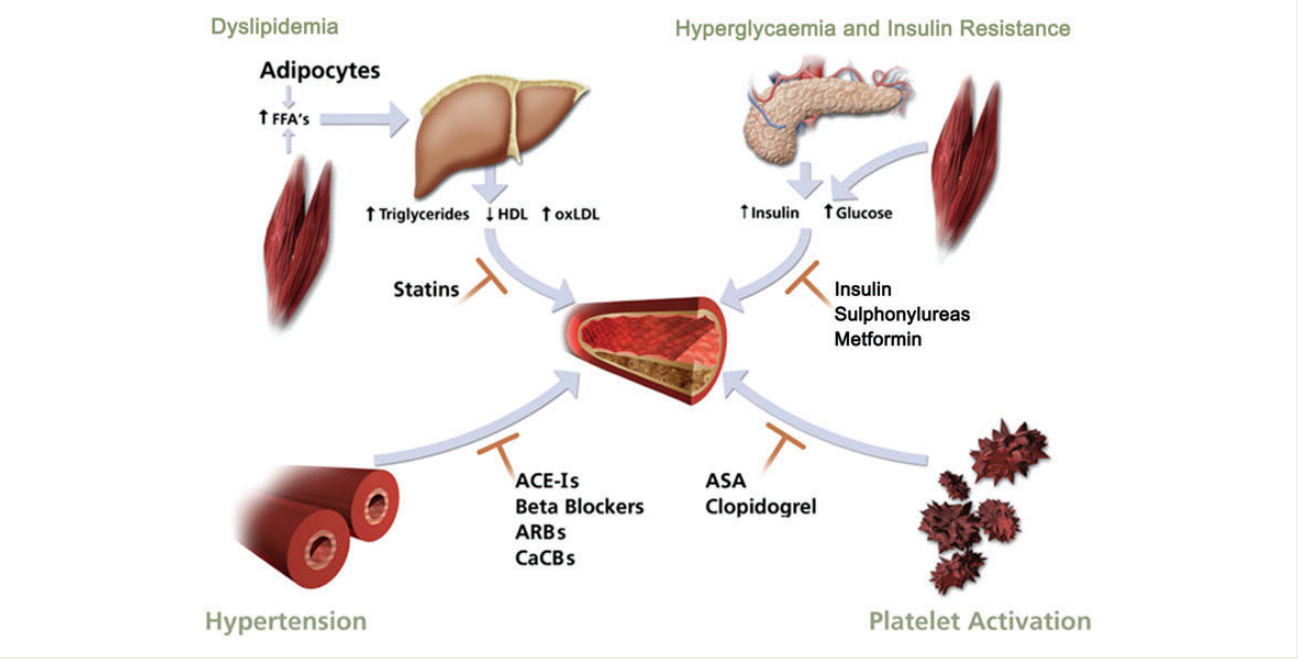

Figure 4 Comprehensive anti-atherosclerotic therapy in diabetes. The pathophysiology of diabetes-related atherogenesis is broad and requires a comprehensive medical strategy to attenuate its progress. Improvements in dyslipidaemia, insulin resistance, hypertension, and platelet activation all have a role in the care of patients with diabetes to minimize the complications of atherosclerosis. Statin therapy provides important risk reduction to diabetic patients with and without diagnosed atherosclerosis. Improvement in glycaemia reduces the rate of myocardial infarction while metformin-mediated improvements in insulin sensitivity provide long-term reductions in cardiovascular death. Antiplatelet therapy including aspirin and thienopyridines have a definitive role in patients with atherosclerosis and a nuanced, individualized role in patients without a diagnosis of previous myocardial infarction, stroke, or peripheral artery disease. Treatment of hypertension significantly reduces stroke and death. With the diagnosis of atherosclerosis, antagonists of the renin–angiotensin system may play a heightened role.

outcomes, likely because the majority of patients required more than one anti-hypertensive agent.[85] Interestingly, the efficacy of treatment of hypertension is not as durable as treatment of hyperglycaemia with metformin. Whereas the benefit of metformin in the first 5 years of treatment persisted and increased over time,[76] the benefit of tight control of blood pressure did not persist once UKPDS had completed.[86] The results suggest that the aggressive treatment of blood pressure must be ongoing for the benefit to be maintained.

There is general agreement about the benefits of 'optimal' blood pressure control, but not about the definition of 'optimal'. Clinical trials that were reported around the time of UKPDS provided some clue as to the appropriate goal level. In the Hypertension Optimal Treatment (HOT) trial, 18 790 patients with diastolic blood pressure between 100 and 115 mmHg were randomly assigned to treatment sufficient to achieve a diastolic blood pressure of 90, 85 or 80 mmHg.[87] In the patients with diabetes, there was a 51% reduction in major cardiovascular events in the 80 mmHg target group compared with the 90 mmHg target group. Similarly, in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, 470 patients with diabetes were randomized to a target diastolic blood pressure of 80–89 mmHg or a diastolic of 75 mmHg.[88] Although cardiovascular events did not differ between groups, all-cause mortality was lower in the more aggressively treated group. Thus, in the Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[89] it was recommended that patients with diabetes have their blood pressure controlled to 130/80 mmHg or lower, although the report admitted that 'available data are somewhat sparse to justify the low target.'

The rationale of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was to determine with definitive clinical trial evidence whether a more aggressive systolic blood pressure target of $<$120 mmHg was superior to a systolic blood pressure target of $<$140 mmHg.[90] In ACCORD, 4733 patients were enrolled and the goals were achieved: at 1 year, the intensive arm had a mean systolic blood pressure of 119.3 mmHg and the standard group had a blood pressure of 133.5 mmHg.[91] After a mean follow-up of 5 years, there was no significant difference in the primary outcome (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), death from any cause, or major coronary disease event. However, there was a significant 40% reduction in stroke. Also, a significant increase in medication-related adverse events was noted. Subjects in the tight arm required 3.4 medications to achieve the target compared with 2.1 medications in the standard group. We await JNC 8 for any change in the recommended target of 130/80 mmHg in patients with diabetes.

The preferred class of anti-hypertensive in patients with diabetes merits consideration. The choice of agent may be predicated on the presence of complications of diabetes. In the absence of complications, ALLHAT, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, demonstrated no difference in

the primary outcome of fatal coronary heart disease or non-fatal myocardial infarction among the chlorthalidone, amlodipine, and lisinopril arms in patients with diabetes.[92] Thus, if the primary goal of treatment is the reduction of blood pressure, then a thiazide diuretic, dihydropyridine calcium-channel blocker, or angiotensin-converting enzyme inhibitor (ACE-I) are acceptable first choices. β-adrenergic antagonists should not be considered as first-line agents for treating hypertension in most patients. A meta-analysis of 12 studies evaluating 94 492 patients found that β-adrenergic blocker therapy was associated with a 22% increased risk for new-onset diabetes, and a 15% increased risk of stroke compared with non-diuretic antihypertensive agents.[93] In contrast, β-adrenergic blocker therapy is recommended for 3 years after myocardial infarction and in the setting of left-ventricular dysfunction, with or without heart failure. Moreover, β-adrenergic blocker therapy, titrated to full dose, is recommended for the treatment of stable angina.[94]

If the goal is secondary prevention of atherosclerotic events, antagonists of the renin–angiotensin system take precedence because of the possible benefits beyond blood pressure lowering. The efficacy of ACE-I therapy has been demonstrated in several large clinical trials. In the Heart Outcomes Prevention Evaluation (HOPE) study, 9297 subjects with atherosclerosis or diabetes and a cardiovascular risk factor were randomly allocated ramipril or placebo.[95] The diabetic subgroup showed significant reductions in MI, stroke, and death, despite a baseline blood pressure of 139/79 mmHg prior to treatment. The ADVANCE trial enrolled 11 140 subjects with diabetes, irrespective of blood pressure, and randomly allocated the subjects to perindopril and indapamide or matching placebo.[96] With a drop of 5.6 mmHg in systolic blood pressure, the perindopril and indapamide combination reduced all vascular events, but not cardiovascular events alone. In the EUropean trial on Reduction Of cardiac events with Perindopril (EUROPA) trial of patients with stable coronary artery disease, perindopril reduced the composite endpoint of cardiovascular mortality, MI, or cardiac arrest, similarly in those with and without diabetes.[97] Interestingly, when the 1502 diabetic subjects of EUROPA were evaluated independently, no benefit could be demonstrated, likely suggesting inadequate power in this sized sample.[98] In other trials of secondary prevention after a cardiovascular event, ACE inhibition has been shown to reduce recurrent stroke in diabetic patients with previous stroke or TIA[99] and reduce mortality in diabetic patients after myocardial infarction.[100–102] Angiotensin receptor blockers (ARBs) have similar efficacy to ACE-I after myocardial infarction. In the Valsartan in Acute Myocardial Infarction Trial,[103] valsartan was as effective as captopril for the primary endpoint of total mortality in the subgroup of diabetic patients with myocardial infarction complicated by left-ventricular systolic dysfunction.[104] In the Losartan Intervention For Endpoint reduction in hypertension study,[105] losartan was found to be superior to atenolol in diabetic patients with end-organ damage for the primary composite endpoint of cardiovascular death, MI, and stroke,[106] and in the Valsartan Antihypertensive Long Term Use Evaluation (VALUE), valsartan was equivalent to amlodipine for the endpoint of cardiovascular morbidity and mortality in hypertensive diabetic patients.[107] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[108] enrolled 25 620 patients with vascular disease or diabetes with end-organ damage and randomized them to ramipril, telmisartan, or the combination. After a median 56 months of follow-up, there was no difference among the groups in the primary outcome of death from cardiovascular cause, myocardial infarction, stroke, or hospitalization for heart failure in the entire cohort and diabetic subgroup.

Inhibitors of the mineralocorticoid receptor have been studied in large trials in patients with congestive heart failure and left-ventricular dysfunction after myocardial infarction. In the Randomized Aldactone Evaluation Study (RALES) trial of patients with severe systolic heart failure, spironolactone reduced mortality by 30% in patients with and without diabetes.[109,110] Two trials have evaluated the use of eplerenone in patients with reduced left-ventricular systolic function, one in patients with mild heart failure and the other in patients after myocardial infarction. In both trials, eplerenone reduced mortality compared with placebo, and patients with diabetes received the same benefit as those without diabetes.[111,112]

Recent trials, however, have cast doubt on the perceived superiority of renin–angiotensin antagonists in patients with diabetes. In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, 9306 subjects with impaired glucose tolerance and established cardiovascular disease were randomized to valsartan or placebo and followed for 5 years. Despite a 2.8/1.4 mmHg difference in blood pressure between the groups, there was no difference in death, myocardial infarction, stroke, and revascularization.[113] Similarly, in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, telmisartan failed to reduce stroke and major cardiovascular events in diabetic patients with recent stroke when compared with placebo.[114] In contrast, the ACCOMPLISH trial in which 60% of patients had diabetes showed that treatment with the ACE-I benzapril in combination with amlodipine significantly reduced cardiovascular events.[115] For now, the usefulness of ACE-I and ARB in diabetic patients with myocardial infarction remains clear, but the preferential role in other settings less so.

Dyslipidaemia

The cornerstone of lipid management in diabetes is the hydroxymethylglutaryl-CoA reductase inhibitors (statins). The landmark Heart Protection Study established the role of statins in the treatment of patients with diabetes.[116] In the 5963 subjects with diabetes and no cardiovascular disease, there were significant reductions in first non-fatal myocardial infarction or death, major coronary events, stroke, and revascularization in the group treated with simvastatin compared with the group treated with placebo. These benefits were recapitulated with atorvastatin in Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm[117] and the Collaborative Atorvastatin Diabetes Study.[118] Statins have an even more profound effect in diabetic subjects preventing recurrent myocardial infarction and a similar benefit in preventing stroke compared with patients without diabetes.[119–121] Thus, patients with diabetes should be treated with a statin. The one exception may be in patients with renal failure, as statins have failed to show efficacy consistently is in diabetic patients undergoing haemodialysis.[122,123] Moreover, high-dose more potent statins have been shown to be superior to a lower dose of the same medication or less-potent statins in two clinical trials, indicating that a high dose of a more potent statin therapy should be used in standard practice.[124,125]

The usefulness of other lipid modification agents, alone or in addition to statins, in patients with diabetes is not established. Early work with fibric acid derivatives alone demonstrated a similar reduction in cardiovascular events in patients with and without diabetes in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial,[126] but more recent data have been less compelling. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized 9795 patients with type 2 diabetes to fenofibrate or placebo,[127] but was unable to show a reduction in the primary outcome of coronary events. The lack of efficacy was posited to an unequal distribution of statin usage. The use of fenofibrate was associated with a reduction in minor amputation,[128] although interpretation of a secondary endpoint without a positive primary endpoint should be done with caution. The use of a fibrate in supplement to statin therapy for all subjects with diabetes was studied in the ACCORD Lipid trial.[129] In this trial of 5518 patients, all patients received open label simvastatin and were randomized to fenofibrate or placebo. After a mean follow-up of nearly 5 years, despite significantly lower triglyceride and higher high-density lipoprotein (HDL) levels in the fenofibrate arm, there was no difference in the rate of major fatal or non-fatal cardiovascular events, stroke, or death. Based on this trial, routine use of a fibrate in addition to statin therapy is not warranted. Some have suggested that fibrates may have value in patients with high triglyceride and low HDL levels,[130] but this remains to be proved prospectively. Similarly, niacin has yet to find a treatment niche when statins are in use. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, 3414 patients with established vascular disease on a statin with low HDL and high triglycerides were randomized to extended release niacin or placebo.[131] Niacin treatment significantly increased HDL, lowered triglyceride, and lowered LDL levels, but there was no difference in the composite of death from coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization or any of the individual components in the entire cohort and diabetic subgroup. For now, the addition of a second lipid modifying medication may be made on an individual basis, but cannot be recommended for all patients with diabetes.

Antiplatelet therapy

The benefit of antiplatelet therapy in patients with diabetes but without evident atherosclerosis has become less clear with time. The current recommendation by the US Preventive Services Task Force and the American College of Chest Physicians is low-dose aspirin for primary prevention in all patients.[132,133] This recommendation is largely based on meta-analyses of many primary prevention trials showing a small benefit of aspirin in the reduction of non-fatal myocardial infarction (about five events per 10 000 patients) offset by a similar increase in gastrointestinal hemorrhage (three events per 10 000 patients).[134–137] However, the data in diabetic patients in particular is not compelling. Two recent trials enrolled only patients with diabetes and found no benefit. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JAPAD) Trial included 2539 patients with diabetes and no history of atherosclerotic disease.[138] There was a non-significant 20% reduction in atherosclerotic events (fatal and non-fatal MI, fatal and non-fatal stroke, and peripheral artery disease). Similarly, in the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, 1276 adults with type 2 diabetes and an ankle–brachial index of <1.0 were randomized to daily aspirin or placebo.[139] In this study, there was no significant difference in the composite outcome of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia; or any of its individual components. A meta-analysis of aspirin treatment in only the diabetic subjects in large primary prevention studies demonstrated a trend towards a 10% reduction in the cardiovascular disease events.[140] Based on the limited data and small, if any benefit, the American Diabetes Association, American Heart Association, and American College of Cardiology Foundation recommend the use of low-dose aspirin in diabetic patients with a cardiovascular disease risk of $>1\%$ per year based on diabetes-based risk calculators like the UKPDS Risk Engine (http://www.dtu.ox.ac.uk/riskengine/index.php) or American Diabetes Association Risk Assessment Tool (http://www.diabetes.org/phd).[140] Thus, diabetes alone is not enough to warrant low-dose aspirin therapy, but use of aspirin may be acceptable when the cardiovascular risk surmounts the 1% per year needed to gain the small benefit of aspirin in primary prevention.

In patients with acute coronary syndromes aspirin significantly reduced the rate of reinfarction, stroke, and death.[141] More potent than aspirin, the P2Y12 inhibitors, have been studied in secondary prevention, both in the acute phase of coronary syndromes and stroke and during stable chronic follow-up. In the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, 19 185 patients with coronary artery disease, cerebrovascular disease, or peripheral artery disease were randomized to aspirin or clopidogrel.[142] A modest 0.5% absolute annual risk reduction was noted. In the diabetic subgroup of 1952 patients, the absolute risk reduction was 2.1%, significantly larger than in subjects without diabetes.[143] However, in The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial of patients with established atherosclerosis or multiple risk factors for atherosclerosis, the addition of clopidogrel to aspirin was no more effective than aspirin alone in the prevention of the composite endpoint of cardiovascular death, MI, and stroke.[144] Following acute coronary syndromes, there is evidence that greater antiplatelet inhibition provides more benefit for patients with diabetes. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated benefit in reducing the composite of cardiovascular death, non-fatal MI, and stroke with the addition of clopidogrel to aspirin in both non-diabetic and diabetic patients with acute coronary syndrome.[145] In TRITON-TIMI 38 trial, patients with acute coronary syndromes undergoing percutaneous revascularization were randomly allocated to clopidogrel or prasugrel. The benefit associated with the more potent prasugrel was significantly greater for subjects with diabetes than those without diabetes, despite no excess bleeding.[28] In the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, patients randomized to prasugrel had a lower rate of recurrent events than those randomized to clopidogrel. In contrast to TRITON-TIMI 38, the patients with diabetes did not have a better result than those without diabetes.[146] Another novel P2Y12 inhibitor, ticagrelor, was tested in patients with acute coronary syndromes and compared with clopidogrel in the Platelet

Inhibition and Patient Outcomes (PLATO) trial. In Plato, ticagrelor was superior to clopidogrel and showed a significant reduction in mortality, but the benefit for subjects with diabetes was not different from the cohort as a whole.[147,148] Further work is needed to clarify these differences among agents and their interaction with diabetes.

The benefit of risk modification in aggregate

Modifications of each of the risk factors brings reductions in cardiovascular adverse events. Intensive modification of every risk factor provides additive benefits. In the Steno-2 trial, 160 patients with type 2 diabetes were randomized to intensive therapy or conventional therapy and followed for up to 13 years.[149] Intensive therapy was defined as haemoglobin A1c $<6.5\%$, total cholesterol <175 mg/dL, fasting serum triglycerides <150 mg/dL, systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg, use of low-dose aspirin, and treatment with renin–angiotensin antagonist. Intensive therapy significantly reduces cardiovascular and total mortality compared with standard treatment. Thus, intensive therapy of all the risk factors for atherosclerosis is life extending and should be pursued.

Indeed, intensive medical therapy is so effective, that investigation for coronary artery disease in asymptomatic patients is unnecessary. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1123 subjects with type 2 diabetes were randomly assigned to adenosine stress radionuclide myocardial perfusion imaging or no screening.[150] Over nearly 5 years of follow-up, there was a cumulative cardiac death or non-fatal myocardial infarction rate of 2.9%, without difference between the two groups. Thus, aggressive use of risk modifying therapies remains the mainstay of therapy. On the other hand, intensive treatment of risk factors, namely hypertension and hyperglycaemia may also associate with increased cardiovascular events in the diabetic population.[70,151] Hence, a cautious approach should be implemented when considering individual therapeutic targets in this setting.

Coronary revascularization

The role of revascularization in diabetes has evolved over the recent years. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial included 2287 patients with significant stable coronary artery disease and compared the outcomes of optimal medical therapy (OMT) with and without percutaneous coronary intervention (PCI).[152] Over a median 4.6 years of follow-up, the addition of PCI to OMT did not reduce death and MI compared with OMT alone, either in the entire cohort or the subgroup with diabetes. Thus, in most patients with stable coronary artery disease, who have preserved left-ventricular function and have not exhibited severe myocardial ischaemia on a stress test, may be treated with optimal medical therapy alone for the reduction in death and MI, unless an acute coronary syndrome develops. The use of PCI for symptom reduction was superior in COURAGE and may be applied on an individual basis, should medical therapy fail. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial provided similar results. In this trial, 2368 patients with type 2 diabetes and heart disease were given intensive medical therapy and randomized to prompt revascularization or expected management.[153] In the revascularization arm, the responsible physician determined the appropriate strategy. Over the course of 5 years of follow-up, there was no difference in survival between the medical therapy and revascularization arms in total, or by type. In a secondary outcome, the patients in the coronary artery bypass portion of the study who underwent surgery had a significantly lower rate of major cardiovascular events (death, MI, or stroke) than those allocated to medical therapy. This may have resulted because the patients in the bypass arm had more triple vessel coronary artery disease (52.4 vs. 20.3%). The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial compared the outcomes in 1900 diabetic subjects with multivessel coronary disease randomly assigned to percutaneous coronary intervention or coronary artery bypass grafting and followed for a median of 3.8 years.[154] Subjects who underwent surgical bypass had an absolute 7.9% reduction in the primary outcome of death, non-fatal myocardial infarction, and non-fatal stroke. Indeed, the reduction in death from any cause was significant by itself, with a 5.4% absolute reduction in all-cause mortality. Thus, in patients with diabetes and multivessel disease who require revascularization, coronary artery bypass surgery is preferred over percutaneous coronary intervention.

Conclusion

Diabetes is a risk multiplier in atherosclerosis. It increases the risk of developing atherosclerosis, the incidence of complications of atherosclerosis, and is associated with poorer outcomes from these events. Health care professionals now have the benefit of a wide variety of clinical trial data supporting specific treatments and targets for patients with diabetes. These include lipid-lowering therapy with statins, blood pressure control, and antiplatelet therapy in patients with increased cardiovascular risk scores. Hyperglycaemia should be treated to a target glycosylated haemoglobin of 7%, with therapy that includes an agent that improves insulin sensitivity, such as metformin. Optimal medical treatment, including risk factor modification, antiplatelet therapy, and antianginal medications is the preferred approach for most patients with diabetes and stable coronary artery disease. Over the last decade, aggressive application of these therapies by care providers has reduced the rate of cardiovascular events in patients with diabetes, ameliorating outcomes in this population. Despite these improvements, the risk of adverse cardiovascular outcomes remains significantly higher in patients with diabetes than those without diabetes. Understanding the pathophysiology of vascular disease in diabetes, as reviewed in Part I of this review will facilitate discovery of beneficial treatments for diabetic patients to reduce this gap in morbidity and mortality.

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