Cardiovascular Disease in Diabetes Mellitus

Risk Factors and Medical Therapy

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KEYWORDS

• Cardiovascular disease • Diabetes • Myocardial infarction • Coronary heart disease • Hyperglycemia • Risk • Therapy

KEY POINTS

- Diabetes mellitus (DM) is a condition on the increase, carrying a high risk of cardiovascular (CV) complications.
- Diabetes carries a higher risk for cardiovascular events in women than in men.
- Clinicians still do not have the ability to precisely and reliably stratify risk among patients with diabetes.
- Treatment of known cardiovascular risks such as hypertension, hyperlipidemia, and smoking is key in decreasing the risk for cardiovascular events.
- Some glucose-lowering drugs may have a more positive impact on minimizing cardiovascular disease, but more research needs to be done to confirm this possibility.

INTRODUCTION

Diabetes mellitus (DM) is a disease on the rise. A 2011 report from the Centers for Disease Control and Prevention indicated that 25.8 million people, 8.3% of the United States population, have DM. Among adults age 65 years or older, 26.9% had diabetes in 2010.[1] Worldwide there are 240 million people with DM, and it is projected that by 2030 there will be 439 million affected by diabetes.[2] The most common cause of death among patients with diabetes is cardiovascular disease, with heart disease responsible for 70% of deaths.[3] The risk of increased cardiovascular morbidity and mortality has been recognized for years, dubbing diabetes "cardiovascular disease equivalent."

The authors have no conflict of interest.

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Endocrinol Metab Clin N Am ■ (2013) ■–■
http://dx.doi.org/10.1016/j.ecl.2013.09.001 **endo.theclinics.com**
0889-8529/13/$ – see front matter

EPIDEMIOLOGY

There is no argument that individuals with diabetes have a significantly increased risk of macrovascular complications, but how accurate is this label of "cardiovascular disease equivalent?" Fifteen years ago a landmark Finnish study attempted to answer this question. A 7-year risk of myocardial infarction in middle-aged patients with diabetes was 20%, similar to that of patients with a previous myocardial infarction.[4] Following this study there have been a flurry of epidemiologic studies arguing for or against the risk equivalence. Results are as varied as the studies themselves. The risk seems to vary by severity of diabetes as well as definition of coronary heart disease (CHD) used. For example, in patients with diet-controlled diabetes, the risk of mortality and myocardial infarction was smaller than that in patients with a previous myocardial infarction.[5,6] On the other hand, diabetic patients treated with glucose-lowering agents had a risk of mortality similar to that of patients who had a previous myocardial infarction, and a much greater risk of death than patients with angina, evidence of ischemia or infarct on electrocardiogram, but no history of an infarct. This risk was disproportionately high in women.[6,7]

In long-standing diabetes, women carried almost twice as high a hazard ratio for all-cause mortality and for death from CHD when compared with men with diabetes and patients with CHD without diabetes. The highest risk of death occurred in patients with both CHD and diabetes: hazard ratio of 4.44 for men and 5.86 for women.[8]

It is clear, therefore, that patients with diabetes are not a homogeneous group. Women are at a higher risk than men. Younger patients and those with shorter, milder disease are at a lower risk of events. Patients with type 1 diabetes may also have a lower risk when young and early in the disease course.[9]

ASSESSING THE RISK OF CARDIOVASCULAR EVENTS

There is significant amount of dispute regarding which parameters allow for most accurate assessment of risk and prediction of cardiovascular event. There is no doubt that chronic hyperglycemia imparts increased risk for mortality and events in both type 1 and type 2 diabetes; however, the association is not linear and is not consistent in all types of vascular disease. In one study, elevated fasting glucose has been found to increase the risk for all types of vascular disease, including ischemic and hemorrhagic stroke.[10] This increased risk of mortality was noted already when fasting glucose was greater than 100 mg/dL, and it was linked to a 6-year shorter life span in a 50-year-old individual with DM. Sixty percent of this risk is attributable to vascular death.[11] On the other hand, other studies show less consistent results in some groups. Postmenopausal women with established CHD and impaired fasting glucose of 100 to 125 mg/dL had no increased risk of coronary events. However, when the old definition of impaired fasting glucose was applied (glucose >110 mg/dL), women had an increased risk of myocardial infarction and cardiac death. Strokes, transient ischemic attacks (TIAs) and congestive heart failure (CHF) were not predicted by impaired fasting glucose by either definition.[12]

Postprandial glucose has been studied extensively as a predictor of cardiovascular outcomes. Hyperglycemia at 1 hour and 2 hours after a standard 75-g oral glucose tolerance test, as well as after a meal challenge, has proved to be a good predictor of cardiovascular events and mortality.[13] This relationship is linear. In some groups such as older adults and women, postprandial glucose may have a better ability to predict mortality than a fasting value, although combination of both fasting and 2-hour glucose may allow for more accurate risk estimation.[13–15] Given that acute

hyperglycemia may cause vasoconstriction, there is a sound physiologic base for concern, even in patients with normal fasting glucose.

Elevation of glycosylated hemoglobin (HbA1c) appears to correlate with mortality and cardiovascular events in a linear manner as well: a 1% increase of HbA1c carries a significant increase in risk (20%–30%) for cardiovascular events or death.[16] This risk exists for coronary artery disease, fatal and nonfatal myocardial infarction and stroke, and perhaps most strongly for peripheral artery disease, in patients with both type 1 and type 2 diabetes.[17] Even in the absence of diabetes a small increase in HbA1c (>5%) is associated with an increased risk of CHD.[18]

Here again, not all data are consistent. In one study of women with no diabetes, elevation of HbA1c did not predict the risk of cardiovascular events.[19] It is controversial whether HbA1c is a better or worse prognosticator of cardiovascular events. However, attempts to lower HbA1C do not consistently lower mortality in all patients, complicating this issue further.[20]

In addition to elevated glucose, patients with diabetes have several other risk factors. Comorbidities such as renal disease, hypertension, dyslipidemia, sleep apnea, obesity, and poor physical fitness all carry a significant increase in cardiovascular risk. Some of the risks, such as macroproteinuria, may be a better predictor of mortality than glucose or HbA1c.[21] This heterogeneity of risks makes event prediction difficult. Unfortunately, treatment of cardiovascular complications is costly and, therefore, precise identification of the most vulnerable patients would be important in early prevention.

Framingham, UKPDS Risk Engine, SCORE, and DECODE are among calculators that have attempted to better estimate risk for individual patients. The results, however, are inconsistent: the accuracy varies in men and women, and none of these risk engines have been validated against a pool of American patients.[22,23]

PATHOPHYSIOLOGY

There are several potential mechanisms through which diabetes causes acceleration of atherosclerosis. Persons with type 2 diabetes have hypertension as well as abnormalities of lipid metabolism and insulin resistance, all of which are linked to increasing cardiovascular risk. Hyperglycemia likely also plays a central role in pathogenesis of vascular diseases, evidenced by the increased prevalence of atherosclerosis in people with type 1 diabetes without dyslipidemia or hypertension.

Within the blood vessels, endothelial cells come into direct contact with high glucose levels and play several key regulatory functions. These cells mediate vasodilation through production of bradykinin and nitric oxide, which acts on smooth muscle, resulting in relaxation and vasodilation. Endothelial cells also regulate vasoconstriction through local production of angiotensin-converting enzyme (ACE), prostaglandins, and endothelin. Vasoconstriction is driven by high angiotensin II levels, inducing smooth-muscle activation and bradykinin breakdown mediated by high levels of ACE. Hyperglycemia disrupts normal production of nitric oxide, leading to decreased blood flow. In addition, elevated levels of nonesterified fatty acids, often present in type 2 diabetes, further contribute by impairing vasodilation.[24]

Hyperglycemia also induces inflammation through stimulation of adipokines and upregulation of toll-like receptors (TLRs) in the endothelium. The usual function of TLRs is triggering both innate and adaptive immune response against a broad range of pathogens. When inappropriately activated, they initiate an excessive white blood cell response, resulting in ischemic reperfusion injury, restenosis, and formation of atherosclerotic plaque.[24]

Hyperglycemia may also play a role in monocytes adhering to a vessel wall and differentiating into macrophages. Glucose modulates the ability of macrophages to take up lipids and become foam cells.[24] This accumulation of lipid cells results in fatty streaks, which later become necrotic in the center and rupture.[25] Matrix metalloproteinases are also induced by hyperglycemia and may be linked to intraplaque hemorrhage, which destabilizes plaque.

There is some evidence that changes in the extracellular matrix resulting from hyperglycemia may cause collagen-matrix remodeling and smooth-muscle cell proliferation, resulting in a protective response of stabilization of a plaque. The same mechanisms may also play a deleterious role in coronary vessel restenosis after intervention.

Furthermore, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia may cause excessive platelet activation and an increase in plasminogen activator inhibitor (PAI-1) levels, a major inhibitor of fibrinolysis. These changes of normal metabolism lead to a prothrombotic state.

Hyperglycemia and an increased level of fatty acids are important factors in inducing oxidative stress and inflammation in the pathogenesis of atherosclerosis, but may not be the only ones. Insulin resistance on a vascular level and a high circulating concentration of insulin may also play a role in acceleration of atherogenesis in diabetes. All of these mechanisms are still not completely understood.

MITIGATING THE RISKS

Intensive Glycemic Control

It has been well established that good glycemic control decreases the risks of microvascular complications. With regard to macrovascular complications, the answer is not as clear. It seems that treating more aggressively early in the course of DM does decrease the risk of myocardial infarction and reduces mortality. In UKPDS, a large study of patients with type 2 DM early in the disease course, there was no difference found in cardiovascular outcomes during the first 10 years between diet-controlled and intensively managed, pharmacologically treated groups. The average HbA1c difference between groups was 7.0% versus 7.9%, which was sufficient to decrease the rate of microvascular complications.[26] During the additional decade of follow-up observation with no intervention, there was a significant reduction of myocardial infarctions and death noted in the original intensive treatment group, despite the fact that the difference in HbA1c levels was lost after the first year of the follow-up study, 11 years after enrollment.[27] Similar results were found in a study of patients with type 1 DM.[28] Reduction of HbA1c from 9.1% to 7.4% early in disease course significantly reduced the risks of any cardiovascular disease by 42% and decreased the risk of strokes, myocardial infarctions, and cardiovascular death by 57% over a 17-year follow-up period.[29]

However, attempts to treat hyperglycemia aggressively in patients with long-standing diabetes did not bring similar positive results. VADT, a study of older men with long-standing diabetes, showed that reduction of HbA1c from 8.4% to 6.9% did not improve cardiovascular outcomes.[30]

Two recent large trials involving populations with previous cardiovascular events or at significant risk are the ADVANCE and ACCORD trials. The ADVANCE trial showed no beneficial effect on the rate of macrovascular events, when HbA1c was brought to 6.5% rather than the standard 7.3%.[31] On the other hand, the ACCORD trial was stopped early because of a 22% higher mortality in intensive glycemic control group.[20] During a 5-year observational follow-up period, patients initially assigned to the intensive treatment group experience a decreased risk of myocardial infarctions, but the

increased risk of mortality persisted[32]; this despite HbA1c increasing from 6.6% to 7.4% in the initial intensive control group while HbA1c remained stable in the standard group (rising from 7.7% to 7.8%). The patients in the intensive group did require a more complicated multidrug regimen. The mortality, however, did not appear to be a direct result of hypoglycemic events.[33] It is also interesting that in the intensive control group, there was a liner relationship between mortality and HbA1c: individuals with higher HbA1c had higher mortality, similarly to what was observed in the UKPDS and DCCT-EDIC trials. One possible explanation for this finding is that disproportionate mortality occurred in a group of individuals who enter the intensive arm with HbA1c higher than 8%, and whose HbA1c remains higher than 8% throughout the course of the trial despite all efforts.[34]

When these and other studies are compiled in a meta-analysis, the results are a little more reassuring. It appears that intensive glycemic control may decrease the risk of nonfatal myocardial infarction, with no positive or negative effect on mortality, strokes, and peripheral vascular disease. However, this reduction in myocardial infarcts carries a price of a 30% increased risk of hypoglycemia.[35–38]

These data indicate the need for individualization of glycemic goals. Intensive therapy may be helpful in reducing cardiovascular events and mortality when initiated in people with shorter, uncomplicated diabetes. In patients with diabetes of longer than 15 years and long-standing complications, risk of tight control may outweigh the benefit.[39] Some investigators suggest that for such patients, an HbA1c goal of 7% to 7.9% may be sufficient to optimize the risk profile for cardiovascular events (**Table 1**).[40]

There is still a significant amount of debate over what are the most appropriate goals and for whom. Part of this discussion also concerns the most beneficial manner of treating diabetes: that is, whether any particular medication or medication combination improves cardiovascular outcomes.

CHOOSING THE RIGHT AGENTS

Metformin is a first-line drug recommended by several professional associations.[41,42] Lactic acidosis is its most feared side effect, although the actual risk is likely overestimated.[43] The UKPDS trial showed that metformin was particularly efficacious, with a 33% risk reduction of myocardial infarctions and 27% reduction of death in comparison with diet therapy.[27] BARI 2D did not show a clear mortality advantage, although patients on insulin sensitizers developed less peripheral artery disease.[44,45] However, this study did not separate the effect of metformin from other sensitizers, so it is difficult to say if the beneficial effect of metformin could have been blunted by the negative effect of other drugs such as rosiglitazone. Metformin has also been associated with decreased mortality in patients with CHF, despite the fact that heart failure is listed as a relative contraindication on the insert package.[46]

Thiazolidinediones (TZDs) are another class of insulin sensitizers, but with a controversial risk profile. It is now well recognized that this class of drugs has a negative effect on heart failure, as it is associated with volume expansion through peroxisome proliferator-activated receptor (PPAR)-γ–dependent pathways. Rosiglitazone created headlines when a significantly increased risk of myocardial infarctions and cardiovascular mortality were discovered.[47] Although a follow-up study showed no mortality effect, the use of TZDs has declined.[48] Favorable data for pioglitazone with regard to decreased risk of myocardial infarctions, strokes, and death did little to restore the reputation of TZDs.[48,49]

Sulfonylureas also appear to have a less favorable profile in comparison with metformin. Although they did decrease myocardial infarctions by 15% and mortality by

Table 1
Major trials: effect of treatment of diabetes mellitus (DM) on cardiovascular (CV) outcomes

Study	Goal	Outcome	Notes
ACCORD[20,32]	Lowering HbA1c to <6% in intense vs standard therapy in high CV group	Increased mortality in intense therapy group	Study stopped prematurely Mortality not related to hypoglycemia
ADVANCE[31]	Lowering HbA1c to <6.5% vs standard therapy in high CV risk group	No decrease in mortality or rate of cardiovascular events	
BARI2D[44,45]	Use of insulin sensitizers vs insulin-provision therapy	No difference in CV outcomes	Analysis of events not broken down further into different class of drugs
DCCT[28]	Intense vs standard therapy (HbA1c of 7.4% vs 9.1%) in type 1 DM early in disease course	No difference in CV events during 7 y of follow-up	Low number of events in both groups (young volunteers: average age 27 y)
DCCT-EDIC[29]	17-y follow-up of patients from DCCT	Lower rates of events including death in intensive therapy group	HbA1c converged in both groups to 7.8%–7.9% at the end of study
Heart 2D 2009	Prandial vs basal insulin therapy	No difference in CV events	Stopped due to lack of efficacy. Less than expected prandial difference
LOOK AHEAD[94]	Intensive lifestyle intervention/weight loss	No effect on CV event rate at 10 y	Stopped prematurely due to futility. 6% in intervention group vs 3.5% body weight loss at the end of the study: difference may have been too small to show CV effect
UKPDS[26,27]	Diet vs medication for control of early diabetes	Lower rates of myocardial infarction and death from any cause in intense treatment group during 2nd decade of follow-up, no difference during the 1st decade	Low number of events during 1st decade of follow-up in both groups
VADT[30]	Lowering HbA1c to 1.5% below standard therapy in older men with long-standing DM and high CV risk	No difference in outcomes	

13% when compared with placebo in UKPDS, there are data indicating that sulfonylureas may not be optimal medications for patients with preexisting CHD and CHF.[27,50] The evidence is far from clear, and there are multiple contradictory reports.[51] Compared with other agents, including insulin, sulfonylureas carry a significant risk of hypoglycemia. It is debatable whether a specific drug has a worse profile than others, but glyburide has shown, although not consistently, to have an increased risk of acute coronary syndrome and cardiovascular death.[52,53] Some investigators suggest that if sulfonylureas must be used, glimepiride is the safest choice.[54]

Insulin is a staple of diabetes treatment. However, treatment of diabetes with insulin leads to a much higher plasma levels of insulin, potentially leading to excessive smooth-muscle activation, which may play a role in atherogenesis.[55] There are also data suggesting worse outcomes in patients with heart failure who use insulin. It is unclear whether this is a function of more severe diabetes affecting mortality or if insulin is in fact a culprit.[56] In well-controlled studies there is no conclusive evidence that insulin administration has a direct beneficial or deleterious effect on the cardiovascular system, apart from reducing hyperglycemia.[51,57]

It is possible that over the next few years clinicians may be encouraged away from insulin toward other classes of drugs. Dipeptidyl-peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists are 2 classes of drugs with promising effects on cardiovascular disease. Preliminary data have suggested that there may be a lower rate of cardiovascular events and mild lipid reduction in patients on DDP-4 inhibitors. The recently published prospective trial SAVOR-TIMI53 found that saxagliptin was not cardioprotective when compared with placebo during a 2-year follow-up for patients with a high cardiovascular risk. On the other hand, there were slightly more hospitalizations for CHF in the saxagliptin group (3.5% vs 2.8% with hazard ratio of 1.27 and $P = .007$).[58] CAROLINA, a study comparing cardiovascular outcomes in patients on linagliptin versus glimepiride, is in progress and will be completed in 2018.

GLP-1 agonists induce weight loss, have a blood-pressure–lowering effect of 2 to 8 mm Hg, and improve lipids, in addition to being linked to decreased rates of cardiovascular events and hospitalizations. In experimental animals, they also improve left ventricular function and reduce infarct size caused by reperfusion.[59] Prospective studies are being conducted to confirm that this is a true effect on the cardiovascular system: the larger among these are MAGNA VICTORIA and LEADER, which will be completed in 2015 and 2016, respectively.

The newest drugs arriving on the market are sodium-glucose cotransporter-2 (SGC-2) inhibitors. Their mechanism of inducing glucosuria promises benefits of modest weight loss and possible reduction in blood pressure of 3 to 9 mm Hg, likely because of its diuretic effect. The effect on lipids is not clear as yet: it appears that treatment with SGC-2 inhibitors may slightly increase high-density lipoprotein (HDL). Data submitted to the Food and Drug Administration show a possible decreased risk of cardiovascular death and events, but long-term data is not yet available.[60] CANVAS, a canagliflozin long-term cardiovascular outcomes trial, and DECLARE-TIMI58, a 6-year cardiovascular outcomes study of dapagliflozin, are both ongoing and will be completed in 2018 and 2019, respectively.

LIPIDS

Lipid-lowering therapy is another critical intervention in improving cardiovascular outcomes. In patients with diabetes it may actually have a more profound effect than intensive glycemic control on lowering mortality and cardiovascular risk.[61] Current standard of care is to treat patients with DM to the goal of a low-density lipoprotein

(LDL) level of less than 100 mg/dL, with an optional goal of less than 70 mg/dL. Patients with DM and CHD should have their LDL level lower than 70 mg/dL. Patients older than 40 years with additional risk factors should be treated with statins as well. Given the recent decline in the cost of statins and benefit of therapy, there is a debate as to whether people younger than 40 years, those with no other risk factors, and good lipid panel should also be treated with statins in the absence of CHD.[62] This proposal is prompted by data that there is a significant reduction in cardiovascular events and mortality with statin use. One study reports a 13% decline in mortality per 1 mmol/L (39 mg/dL) decrease in LDL, with a 21% reduction in major vascular events per 1 mmol/L reduction in LDL-cholesterol in people with diabetes over a period of 4 years.[63] There was no evidence of harm.[64] This treatment effect is consistent with what is observed in patients with no DM: risk reduction is effective. When results were adjusted for baseline risk, diabetic patients benefited more in both primary and secondary prevention, even though lipid reduction was similar in both groups.[65]

Fibrates have also been studied extensively, with mixed results.[66,67] In the FIELD study when fibrates were compared with placebo, there was no decrease in events, likely because of high statin use in the placebo arm, but men with low HDL and triglycerides higher than 200 mg/dL benefited from a reduction in cardiovascular events.[68] In ACCORD, fibrates as an add-on therapy to statins appeared to also have benefited men with low HDL with and without hypertriglyceridemia, whereas women might have been harmed.

Data on use of ezetimibe are still not clear. While it does lower LDL, as yet no results from prospective studies with regard to morbidity and mortality outcomes are available for ezetimibe alone or as add-on therapy. It is reassuring that at least one group found no difference in the rate of events on comparison with statins: results for patients with diabetes did not differ from the rest of the cohort.[69]

Fish oil and omega-3 fatty acid supplements enjoy popularity among physicians and lay public alike. Fish oil is an effective treatment for hypertriglyceridemia, a disorder frequently coexisting with type 2 diabetes. Earlier studies in the cardiovascular literature suggested a possible mortality decrease in patients with heart disease. However, patients with early diabetes and high cardiovascular risk did not reduce their risk of cardiovascular events or mortality by using 1 g of fish oil per day.[70]

HYPERTENSION

Hypertension is a frequent comorbidity in patients with diabetes, especially with type 2 diabetes or type 1 diabetes associated with renal disease. It significantly increases cardiovascular risks, especially strokes. Current American Diabetes Association (ADA) guidelines call for treatment of hypertension when blood pressure is higher than 140/80 mm Hg. Lowering blood pressure to less than 130/80 mm Hg is advised in younger patients if it “can be achieved without undue treatment burden.”[41] This figure represents a change from previous guidelines whereby blood pressure goals were less than 130/80 mm Hg.[71] Such a change is a positive one and reflects current data, which show a clear benefit derived by lowering the blood pressure below the threshold of 140 mm Hg. ADVANCE is a clear example of this. Reduction of blood pressure from 141/77 to 135/75 mm Hg with a fixed dose of perindopril and a diuretic indapamide versus placebo resulted in an 18% reduction of cardiovascular death and a significantly lower number of coronary events.[72]

Another recent large prospective study, ACCORD, showed that lowering systolic blood pressure (SBP) to less than 120 mm Hg did not improve mortality. Risk of stroke was diminished, however, from 0.53% to 0.32% yearly, at the price of

doubling the rate of serious side effects (from 1.3% to 3.3%) such as syncope and hyperkalemia.[73]

A recent meta-analysis of patients with DM and prediabetes suggested that an SBP of 130 to 135 mm Hg may be optimal. Compared with blood pressure of 140 mm Hg, SBP of less than 135 mm Hg reduced mortality by 10% and strokes by 17%. There was no further reduction in microvascualar complication, mortality or CV events, with exception of strokes when SBP was lowered to <130 mm Hg. Reducing blood pressure to less than 135 mm Hg carried a 20% increased risk of serious events, with a 40% increase with SBP lower than 130 mm Hg.[74]

Although patients with diabetes often require multiple medications to control blood pressure, blocking the renin-angiotensin system seems to decrease mortality and the risk of complications in comparison with other antihypertensive agents. Current guidelines recognize this, and recommend the use of ACE inhibitors or angiotensin receptor blockers in the treatment of hypertension in diabetes.[41] Enalapril has been shown to be superior to nisoldipine in reduction of myocardial infarctions in patients in with poorly controlled diabetes.[75]

ASPIRIN

The role of aspirin in the treatment of cardiovascular disease is well established. However, data on the use of aspirin for primary prevention is less clear. There are several prospective studies indicating to a lack of mortality benefit in the general diabetic population.[76,77] Results of subset data analysis and meta-analysis are somewhat inconsistent. Some studies find a decreased risk of fatal and nonfatal strokes and myocardial infarctions through use of low-dose aspirin only in older patients, whereas others show a similar risk reduction only in men.[75,78] One meta-analysis reported a decreased rate of major cardiovascular events and calculated that 92 patients would need to be treated to prevent 1 major cardiovascular event. There was also evidence of harm, mostly from bleeding, in 1 out of every 526 treated patients. Interestingly there was no benefit when each of the events (strokes, myocardial infarctions, mortality) was evaluated separately.[79] Decreased mortality with low-dose aspirin has been found in a study of patients with an average age of 60 years, with the most significant benefit in older and male participants.[80]

With such inconsistency in the literature, it is not surprising that various professional associations differ in their recommendations with regard to the most appropriate age at when to start aspirin in diabetes for primary prevention. Whereas the ADA recommends 75 to 162 mg aspirin for men older than 50 and women older than 60 with an additional major risk factor for cardiovascular disease, the American Heart Association advocates starting therapy for patients older than 40 with risk factors.[81] The results of ASCEND and ACCEPT-D are expected to clarify this issue.

DIAGNOSIS OF CHD IN ASYMPTOMATIC PATIENTS

There is no consensus on how to approach screening of a patient with diabetes and no symptoms of coronary artery disease, yet it is a relevant issue in practice when patients ask if they are safe to start an exercise program. Clinically significant CHD was reported in 20% to 25% of asymptomatic patients with type 2 diabetes when tested by various modalities.[82] However, whether testing is beneficial and which tests to use are unclear. Exercise stress testing with an electrocardiogram is relatively inexpensive and has a 97% negative predictive value. On the other hand, a positive predictive value is less helpful. There is also a practical limitation: some patients may not be able to complete a treadmill test because of obesity, deconditioning, or arthritis.[83]

Using coronary artery calcium scores (CACS) in patients with diabetes can have pitfalls. Asymptomatic patients with a low score of less than 100 had a 21% prevalence of CHD. When identified as low to intermediate risk by the Framingham Risk Score, a CACS score greater than 40 was an independent predictor for atherosclerotic events.[84] In the general diabetic population, an even lower CACS score of 10 or more has been shown to predict all-cause mortality and cardiovascular events with high sensitivity but low specificity. Conversely, a score of less than 10 has an excellent negative predictive value.[85]

Screening patients with adenosine-stress radionuclide myocardial perfusion imaging is widely accepted, although it does not appear to result in event reduction.[86] On the other hand, prompt revascularization in optimally medically managed patients did not result in improved outcomes or survival.[44] Of note, optimally medically managed patients with angina symptoms and those with silent ischemia did not fare any differently.[87]

REVASCULARIZATION

Although there were no differences in outcomes between patients receiving prompt revascularization and those on medical therapy in the BARI 2D trial, a group with the biggest improvement in survival was patients who had coronary artery bypass grafting (CABG).[44] The FREEDOM trial confirmed that for patients with DM and multivessel CHD, CABG was a better option than percutaneous coronary intervention (PCI) stenting. During a 5-year follow-up, the CABG group had a significantly lower mortality (10.9% vs 16.3%) and fewer myocardial infarctions (6.0% vs 13.9%). The downside was a significantly higher incidence of strokes in the postoperative period in the CABG group, 5.2% versus 2.4%.[88] Similar results were found in the past in a meta-analysis study.[89] Because the analysis incorporated studies using non–drug-eluting stents, as the technology improved the results were called to question. FREEDOM, however, compared CABG with PCI using mostly drug-eluting stents.

Men and women with diabetes treated with revascularization have similar risks of myocardial infarction, cardiovascular accidents, and death. Women, however, have more residual angina symptoms and poorer functional status even if they have less anatomic disease before revascularization.[90] After PCI stenting to a single lesion, diabetic patients have worse outcomes when compared with patients without DM. These patients are at increased risk for needing revascularization of the stented lesions during the first year after the procedure, and have an increased risk for cardiac death and myocardial infarctions during 5 years following the procedure.[91]

SUMMARY

Overall, the advanced made in care of patients with diabetes and patients with CHD are encouraging. The mean predicted risk for CHD in the entire population of 7.2% in 1999 to 2000 has dropped to 6.5% in 2009 to 2010. Risk of a cardiovascular event has also fallen from 9.2% to 8.7%, despite an increase in the prevalence of DM. Blood-pressure control, smoking cessation, and improvement in HDL-cholesterol appear to be linked to this improvement. On the other hand, minorities such as African Americans and Mexican Americans still appear to be vulnerable populations.[92]

Encouraging lifestyle modifications such as healthy diet, weight reduction, and exercise is a commonsense approach that has been a cornerstone of diabetes prevention and treatment for many years. Although as little as 5% weight loss results in improvement of metabolic parameters, the recently completed LOOK AHEAD trial

Box 1
Treatment strategies proved to improve cardiovascular outcomes

Lowering HbA1c to less than 8%: benefit of further lowering is controversial

Blocking angiotensin-renin system

Blood-pressure control to lower than 140/80 mm Hg

Low-dose aspirin in older individuals, especially men

Aggressive lipid-lowering therapy to low-density lipoprotein less than 100 mg/dL for primary prevention and less than 70 mg/dL for secondary prevention

Coronary artery bypass grafting is better that percutaneous coronary intervention in treatment of multivessel coronary artery disease

shows that it is not enough to decrease the risk for cardiovascular events in patients with diabetes.[93,94]

To date, it appears that multifactorial therapy including reduction of lipids, renin-angiotensin system suppression, personalized glycemic control, and the use of aspirin in selected patients may be the most effective way to reduce the cardiovascular complications of diabetes (**Box 1**).[61] Early diagnosis and interventions with a treat-to-target approach have been shown to be beneficial over the long term in patients with both type 1 and type 2 diabetes.

ACKNOWLEDGMENTS

Many thanks are extended to Dr Jose Enrique Garcia and Dr Zahid Ahmad for their invaluable input in editing this article.

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