Case: Dan, a white 46-year-old man, was discharged from the hospital one week ago after sustaining a myocardial infarction during his admission. He was admitted after he experienced severe shortness of breath while shoveling the snow in his driveway. He was also diagnosed as having hypertension, type 2 diabetes mellitus, and hyperlipidemia. During his hospital stay, he had percutaneous intervention, with stents placed in two arteries.
When Dan came to the hospital, he believed he was basically healthy, and he was taking no medications. He now has a list of problems and eight medications that he needs to take. He is feeling overwhelmed! He is also aware that, as a result of heart disease, only a few of the men in his family have lived past age 55.

The present article reviews strategies for reducing risk factors to prevent diabetes mellitus-related macrovascular disease in patients such as Dan.

**General risk factors**

Diabetes mellitus is associated with a two-fold to four-fold increased risk of cardiovascular disease and stroke. A combination of pathophysiologic conditions increases the risk for macrovascular events in patients with diabetes mellitus—especially those with insulin resistance. Atherosclerosis, increased platelet adhesion, hypercoagulability, impaired nitric oxide production, and increased free radical formation are believed to be the main contributors to increasing this risk.

Atherosclerosis is a buildup of plaque in the arteries that is initiated by chronic inflammation and injury to the arterial wall. Endothelial injury and inflammation lead to monocyte and lipid infiltration into the endothelial wall and formation of foam cells. Foam cells then stimulate proliferation of macrophages and T lymphocytes, resulting, in turn, in the proliferation of smooth muscle cells and the formation of collagen. Finally, a lipid-rich atherosclerotic lesion with a fibrous cap is formed. Rupture of this lesion leads to an acute vascular infarct.

Risk factor reduction includes lifestyle management, blood pressure control, lipid management, glucose control, tobacco cessation and antiplatelet therapy.

**Lifestyle management**

Management of lifestyle for patients with diabetes mellitus consists of medical nutritional therapy and aerobic exercise. For example, weight loss of 5% to 10% has been associated with improvement in glucose level, lipid level, blood pressure, and cardiovascular risk. Daily dietary allowances, as recommended by the American Diabetes Association (ADA), are noted in Table 1. The ADA recommends moderate exercise for at least 150 minutes per week spread out over at least three days.

In large randomized controlled trials, antioxidants have not been shown to produce benefits in patients with diabetes mellitus. Thus, antioxidants are not recommended in this patient population.

**Blood pressure control**

Management of hypertension and hyperlipidemia has been associated with improved outcomes in patients with diabetes mellitus. Research indicates that the most effective approach to decreasing cardiovascular mortality in these patients is to address hypertension first, then hyperlipidemia, and finally glucose control. However, studies have shown that physician priorities are often the reverse of this approach.

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommended daily allowance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>20-30%</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg</td>
</tr>
<tr>
<td>Fiber</td>
<td>&gt;14 g per 1000 kcal</td>
</tr>
</tbody>
</table>

Effective management of hypertension reduces the risk of cardiovascular complications by 30% to 40%. In the UKPDS, this reduction in risk was accomplished with a mean decrease in blood pressure from 154/87 mm Hg to 144/82 mm Hg.

The ADA recommends a blood pressure goal of less than 130/80 mm Hg in most patients with diabetes mellitus, with a target of less than 125/75 mm Hg in those patients with nephropathy. The systolic blood pressure goal of less than 130 mm Hg has not been firmly established in controlled trials. However, the diastolic blood pressure goal of less than 80 mm Hg has been associated in controlled trials with a reduction in cardiovascular events by 50% in patients with diabetes mellitus.

The ADA recommends using an angiotensin-converting enzyme (ACE) inhibitor as first-line therapy—and an angiotensin receptor blocker (ARB) if the ACE inhibitor is not tolerated. ACE inhibitors are recommended as first-line therapy because of improved cardiovascular outcomes and reduction in proteinuria, in addition to improved blood pressure control, high-risk patients with diabetes mellitus.

Second-line therapy recommended by the ADA is the addition of a thiazide diuretic in patients who have a glomerular filtration rate (GFR) greater than 30 mL per minute, and a loop diuretic in patients who have a GFR less than 30 mL per minute.

Typically, a patient will need three...
or four agents to control blood pressure, including ACE inhibitors, ARBs, \(\beta\)-blockers, calcium channel blockers, and thiazide diuretics. The most important part of blood pressure control is not the agent that is used, but the goal that is obtained.

**Lipid management**

According to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, low-density lipoprotein (LDL) cholesterol is the primary target for controlling hyperlipidemia. The LDL goal is less than 100 mg per deciliter in patients at “high risk” (ie, patients with at least two risk factors but no history of cardiovascular disease or diabetes mellitus), and patients with diabetes mellitus but no other risk factors, and less than 70 mg per deciliter in patients at “very high risk” (ie, patients with cardiovascular disease or diabetes mellitus plus one risk factor). If the LDL target is not achieved with maximally tolerated statin therapy, a reduction of LDL by 30% to 40% is acceptable.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the treatment of choice for lowering LDL levels. Typically, a moderate dose of statin medication will decrease the LDL level by 30% to 40%. Each doubling of the statin dose will decrease the LDL level by another 6%.

Reductions of LDL levels caused by statin therapy have been associated with decreases of 27% in coronary events, 24% in stroke, 22% in major vascular events and 17% in revascularization procedures.

 Patients with type 2 diabetes mellitus (T2DM) typically have the diabetic lipid triad of increased triglyceride level, decreased high-density lipoprotein (HDL) cholesterol level, and increased concentration of small, dense LDL particles. Compared to large, buoyant LDL particles, small, dense LDL particles have greater endothelial permeability, are more easily oxidized and glycated, and are more able to bind to proteoglycans on the vessel wall.

Many patients may have cardiovascular events even with normal LDL levels. Approximately 30% of patients who have a cardiovascular event have an LDL level that is considered to be at goal.

In patients with triglyceride levels above 200 mg per deciliter, a secondary target for treatment is non-HDL cholesterol. The ATP III non-HDL goal is 30 mg per deciliter more than the LDL goal.

Combination therapy of niacin with a statin (ie, simvastatin or lovastatin) has been shown to result in improvement in all cholesterol markers and other biomarkers, as well as in regression of atherosclerosis and in a 60%-to-70% decreased risk of cardiovascular disease.

Fibrate medications are also helpful in decreasing triglyceride levels and in changing LDL from small, dense particles to large, buoyant particles.

In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), gemfibrozil decreased cardiovascular events by 30% to 40% in patients with diabetes mellitus and by 22% in patients without diabetes mellitus. However, gemfibrozil—in combination with a statin medication—carries an increased risk of myalgias and rhabdomyolysis.

Although fenofibrate is not associated with an increased risk of rhabdomyolysis, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that fenofibrate did not improve the primary outcomes of nonfatal myocardial infarction and cardiovascular death.

Other medications that may be useful for lipid management in patients with diabetes mellitus are bile acid resins. In addition to having cholesterol-lowering effects, the bile acid resin colesevelam hydrochloride has been associated with a decrease in glycosylated hemoglobin (HbA\(_1c\)) level by 0.5%, as well as with
a decrease in fasting plasma glucose level. Concerns regarding bile acid resins are gastrointestinal adverse effects, increased risk for drug-drug interactions, and a possible increase in triglyceride levels.

**Other lipid markers**

Other lipid markers have been linked to cardiovascular events in patients with diabetes mellitus. Apolipoprotein B (ApoB) is a marker of total atherogenic particle concentration that reflects cardiovascular risk even when patients are on statin therapy and have normal LDL levels.

The ATP III guidelines recommend an ApoB goal of less than 90 mg per deciliter in patients at high risk and less than 80 mg per deciliter in patients at very high risk.

Lipoprotein (a) is a marker that interferes with fibrinolysis and is a prothrombotic factor. Testing for lipoprotein (a) may be useful in patients with premature or unexplained cardiovascular events. Testing for high-sensitivity C-reactive protein, an inflammatory marker, has been shown to be useful in patients who are at intermediate risk for cardiovascular events. Assessment of LDL particle size and number may also be useful in patients at intermediate risk.

These lipid marker tests, which are expensive, alter management in only a subset of patients. You may want to consider these tests when you have a patient with a low risk for cardiovascular disease but a borderline cholesterol profile or a high risk for cardiovascular disease but a low cholesterol profile.

**Glucose control**

Multiple studies have demonstrated an association between poor glycemic control and risk for cardiovascular complications in patients with diabetes mellitus. However, there is a lack of evidence showing improvement in the risk of cardiovascular disease with intensive management of hyperglycemia in patients with T2DM.

Some recent studies have suggested an increased risk of mortality in patients using intensive glucose control. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which cardiovascular data from more than 10,000 patients with T2DM were examined, was stopped prematurely because of increased mortality associated with the intensive treatment arm. Yet, other trials have found no statistically significant difference in cardiovascular events or mortality between patients using intensive glucose control and those not using intensive glucose control.

In subanalyses of data in the ACCORD trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT), cardiovascular events were found to be decreased in patients who had lower baseline HbA1c values and shorter durations of diabetes mellitus. This finding emphasizes the benefits of starting aggressive therapy early in the course of diabetes mellitus in an effort to prevent complications.

The ADA 2010 Clinical Practice Recommendations recommend an HbA1c goal of less than 6.5% or as close to normal (<6.0%) as possible without increasing the risk for hypoglycemia.

The occurrence of severe hypoglycemia may be part of the explanation for the increased rate of death observed in patients using intensive glucose control in the ACCORD trial.
Severe hypoglycemia may trigger myocardial infarction, stroke or arrhythmia. Hypoglycemia stimulates the sympathetic nervous system and increases levels of catecholamines, which, in turn, increase heart rate, blood pressure and oxygen demand on the heart. In addition, stress on the arterial wall may contribute to plaque destabilization and rupture.

Intensive glucose control for patients with diabetes mellitus was shown in the Diabetes Control and Complications Trial (DCCT)/EDIC—Epidemiology of Diabetes Interventions and Complications Study to decrease the risks of heart disease, stroke and death by 40% to 50% in patients with type 1 diabetes mellitus. However, the UKPDS found only a nonsignificant decreased risk of about 16% in myocardial infarction and sudden death in patients with T2DM undergoing intensive glucose control. The UKPDS also found an 18% reduction in combined fatal and nonfatal myocardial infarction for every one point decrease in HbA1c.

Recent evidence suggests that trials of intensive glucose control in patients with T2DM may not have lasted long enough to reveal the benefits of the intensive treatment. Follow-up studies 10 years after the initial trials of the DCCT and UKPDS noted continued and significant cardiovascular risk reductions.

In the UKPDS follow-up analysis—despite a convergence of HbA1c values in the intensive and nonintensive treatment groups one year after therapy—risk reductions for microvascular disease in the intensive treatment group remained significant. Furthermore, significant risk reductions for myocardial infarction and death from any cause emerged at follow-up in the intensive treatment group.

These data suggest that early intensive management of hyperglycemia may produce long-lasting effects in decreasing risk for macrovascular complications—the so-called “legacy effect.” Future trials are needed to examine data over longer periods to verify that intensive glucose control has a significant impact on reducing the risk of macrovascular disease.

Medications that have been shown to decrease the risk of cardiovascular events in patients with diabetes mellitus include metformin, the thiazolidinedione (TZD) drugs pioglitazone hydrochloride and rosiglitazone maleate, acarbose, and repaglinide. Metformin has been associated with a 30% decrease in cardiovascular mortality and appears to produce long-lasting effects.

The use of TZDs is controversial in terms of risks vs benefits. Because TZDs are associated with fluid retention and worsening of congestive heart failure, they should not be used in patients at risk of these conditions. In some recent trials, pioglitazone has been shown to have cardiovascular benefits, and both pioglitazone and rosiglitazone have been associated with no increased risk of cardiovascular disease.

Postprandial hyperglycemia has been associated with cardiovascular risk and outcomes. Glucose levels one to two hours after oral challenge have proven to be a powerful predictor of cardiovascular risk. Postchallenge hyperglycemia has also been positively correlated with carotid intima-media thickening. Treatments with acarbose and repaglinide have been associated with, respectively, a reduction in cardiovascular events and a regression of carotid intima-media thickness.

Tobacco cessation

Tobacco use increases the risk of both microvascular and macrovascular complications in patients with diabetes mellitus. The risk for cardiovascular disease in smokers with diabetes mellitus is as much as 14 times greater than that from smoking or diabetes mellitus alone.

Assisting patients in their battles for smoking cessation is important. Multiple options for assistance with smoking cessation exist, including nicotine gum, nicotine patches, nicotine inhalers, buproprion, varenicline, behavioral therapy and alternative medical therapies.

Antiplatelet therapy

Aspirin-based antiplatelet therapy is recommended for patients with diabetes mellitus who are aged more than 40 years—with or without a history of cardiovascular disease. The current recommended aspirin dosage is 81 mg daily.

The efficacy of aspirin as primary prevention was validated by the Physician’s Health Study, in which cardiovascular disease was decreased by 40% compared to patients not taking aspirin.
Table 2

Take-home points: Preventing diabetes mellitus-related macrovascular disease

1. Diabetes mellitus is associated with a two-to-four-fold increased risk of cardiovascular disease and stroke.
2. Risk factor reduction is the most important therapy for prevention of macrovascular disease in patients with diabetes.
3. The most effective approach to decreased cardiovascular mortality is to address hypertension first, then hyperlipidemia, and finally glucose control.
4. The most important part of blood pressure control is not the agent that is used but that the goal is obtained.
5. Patients with type 2 diabetes typically have the diabetic lipid triad of increased triglycerides, decreased HDL, and increased small dense LDL particles.
6. A secondary cholesterol target is Non-HDL if LDL optimized and TG are >200 mg/dl.
7. Combination of niacin with a statin has shown improvement in all cholesterol markers and other biomarkers, regression of atherosclerosis, and decreased risk of cardiovascular disease by 60-70%.
8. Intensive glucose control early in the disease may decrease risk for cardiovascular disease.
9. The ADA recommends a goal A1c of <6.5%, or as close to normal as possible (<=6.0%), without increasing the risk for hypoglycemia.

Other studies examining aspirin’s role in primary and secondary prevention have shown a decreased risk for myocardial infarction by 28% to 36%. No difference has been reported in cardiovascular outcomes with the treatment of aspirin vs clopidogrel bisulfate.

Final notes

Because Dan has already had a cardiovascular event, he is at very high risk for future cardiovascular events. Risk factor reduction is prudent in Dan’s case. Lifestyle management is the most important factor to address, with a heart-healthy diet and aerobic exercise of at least 150 minutes per week.

Dan’s blood pressure needs to be decreased to less than 130/80 mm Hg. Achieving this goal will probably require two to three medications, including an ACE inhibitor or ARB. Dan will also need to be on statin therapy and possibly another cholesterol medication to achieve the recommended LDL level of less than 70 mg per deciliter and the recommended non-HDL level of less than 100 mg per deciliter. Early intensive blood glucose control needs to be established with either oral medications or insulin. Baby aspirin is also recommended in Dan’s case.

The main take-home points regarding prevention of macrovascular disease in patients with diabetes mellitus are shown in Table 2. Pharmacologic treatment for such patients can be overwhelming, particularly for someone who was previously taking no medications. Therefore, lifestyle management should be emphasized, because if the patient is able to exercise and lose about 5% to 10% of his or her body weight, some medications may be discontinued.

References


