Cardioprotective Strategies for Patients with Type 2 Diabetes

Case Study and Commentary, *Subbulaxmi Trikudanathan, MD, and Graham T. McMahon MD, MMSc*

Abstract

- *Objective:* To review evidence-based measures for reducing cardiovascular (CVD) risk in patients with diabetes.
- *Methods:* Review of the literature.
- *Results:* Most patients with diabetes will require at least 1 oral hypoglycemic drug, and almost all will ultimately require insulin. Until further data emerge, the most appropriate initial choices remain metformin and a sulfonylurea, moving to metformin and long-acting insulin when glycemic control is suboptimal on maximal dose therapy. Almost all patients should be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. In the absence of contraindications, 81 mg of aspirin should be given to all patients with diabetes who are age 40 or older. For patients with diabetes whose lipids are not at target range, nonpharmacologic interventions (diet and exercise) remain first-line therapies. Lowering low-density lipoprotein cholesterol is the first priority in treating diabetic dyslipidemia. Statins are the agents of first choice, followed by fibrates or ezetimibe.
- *Conclusion:* CVD should be a primary concern for patients with type 2 diabetes and the physicians who care for them. Clinicians need to be sensitive to the challenges these patients face in making therapeutic lifestyle changes and be adept at navigating the polypharmacy that follows from targeting multiple CVD risk factors.

Type 2 diabetes is associated with a significant excess risk for cardiovascular morbidity and mortality. Even with the best medical therapies to control blood glucose, diabetic patients have poorer cardiovascular outcomes than nondiabetic individuals. The risk for a coronary event or stroke is 2 to 6 times higher in the diabetic population than in the general population [1,2]. Mortality for diabetic patients is higher after myocardial infarction (MI) [3] and cardiac revascularization [4]. Even hyperglycemia at the time of an acute MI is associated with increased mortality regardless of a prior diagnosis of diabetes. In their systematic review, Capes et al [5] calculated a 3.9-fold higher mortality rate for those whose blood glucose level was between 110 and 150 mg/dL compared with normoglycemia, with higher values associated with an incremental risk of heart failure and cardiogenic shock. Morbidity and mortality from stroke also are substantially increased; patients with diabetes are 3 times more likely to die as a consequence of a stroke and have a higher risk of permanent neurologic sequelae [6].

There is increasing evidence that cardiovascular disease (CVD) risk can be reduced in patients with diabetes. Although glycemic control remains the key component of diabetes care, identification and management of other CVD risk factors such as hypertension and dyslipidemia are also vital. The American Diabetes Association (ADA) recommends at least annual screening for CVD risk factors (dyslipidemia, hypertension, family history of premature coronary disease, presence of microalbuminuria) and as well as tight treatment goals for glycemia, blood pressure, and serum lipid levels (**Table 1**) [7]. The American Heart Association [8] and National Cholesterol Education Program (NCEP) [9,10] have released similar guidelines recommending that patients with diabetes be treated as high risk and advocating more rigorous lipid and blood pressure targets for both primary and secondary prevention of cardiovascular events if these screening tests reveal abnormalities.

CASE STUDY

Initial Presentation

A 59-year-old woman with type 2 diabetes is referred to an endocrinology clinic for advice on how to lower her risk for CVD.

History

The patient has a 7-year history of type 2 diabetes, currently being treated with maximal doses of metformin (2500 mg/day) and glipizide (40 mg/day). She is also taking ramipril (2.5 mg/day) for mild hypertension. She reports that she does not routinely check her blood glucose level.

From the Department of Medicine, St. Elizabeth's Medical Center, and Tufts University School of Medicine, Boston, MA (Dr. Trikudanathan); and the Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA (Dr. McMahon).

Table 1. Treatment Goals for Adults with Type 2 Diabetes

Glycemic control	
Glycosylated hemoglobin	< 7.0%
Preprandial plasma glucose	90–130 mg/dL
Peak postprandial plasma glucose	< 180 mg/dL
Blood pressure	< 130/80 mm Hg
Lipids	
Low-density lipoprotein	< 100 mg/dL
Triglycerides	< 150 mg/dL
High-density lipoprotein	> 40 mg/dL

Adapted from American Diabetes Association. Standards of medical care in diabetes–2008. Diabetes Care 2008;31 Suppl 1:S12–54.

At a recent primary care visit, the patient was told that her fasting lipid studies were abnormal and that she should start treatment with a cholesterol-lowering medication. The patient is concerned about her risk for heart disease since her father died at age 57 after an acute MI. However, she is also worried about the safety of medications for lowering cholesterol, having heard that muscle damage is possible. Although the patient previously quit smoking but relapsed 8 months ago. She drinks a glass or 2 of wine with dinner most nights. She is a professor at a local university, not married, and travels in her spare time. She enjoys gardening but engages in no aerobic exercise.

Physical Examination

On examination, the patient weighs 212 lb and is 5'7" (body mass index [BMI], 33.2 kg/m^2) with a waist circumference of 34 in. Blood pressure is 136/86 mm Hg in the right arm sitting, with a regular heart rate of 78 bpm. Fundoscopy is unremarkable. Examination reveals no carotid bruits and no acanthosis nigricans. Cardiorespiratory examination is normal. The abdomen is normal and without striae; there is no indication of a secondary cause for her diabetes. Peripheral pulses are intact and normal. Monofilament and vibratory testing of the feet is normal.

Laboratory Evaluation

Results from laboratory studies performed 6 weeks earlier, in advance of the patient's most recent primary care visit, are:

- Glycosylated hemoglobin (HbA_{1c}), 7.5%
- Total cholesterol, 225 mg/dL
- Low-density lipoprotein (LDL) cholesterol, 142 mg/dL
- High-density lipoprotein (HDL) cholesterol, 39 mg/dL
- Triglycerides, 220 mg/dL
- Urine albumin-to-creatinine ratio, 12 mg/g

- **How does this patient's diabetes contribute to her risk for CVD?**

Type 2 diabetes exacerbates traditional modifiable risk factors for CVD (eg, hyperlipidemia, systolic hypertension, cigarette smoking), and according to the UKPDS risk engine (available at www.dtu.ox.ac.uk), this patient's 10-year risk of a coronary event is approximately 20%. Data from trials such as the Multiple Risk Factor Intervention Trial (MRFIT) reveal that the cardiovascular risk associated with diabetes is equal to or greater than the risk in the presence of 2 traditional risk factors. Each additional risk factor caused a greater incremental rise in risk among individuals with diabetes than those without [11]. It is now apparent that adults with diabetes without known cardiac disease have the same risk of a cardiovascular event as nondiabetic adults with a history of MI [12].

The etiology of CVD in diabetic patients is multifactorial. However, it is clear that longer duration of diabetes during adulthood (the years of exposure to diabetes before age 20 add little to the risk of macrovascular disease), greater degree of hyperglycemia, and the presence microalbuminuria correlate with greater risk of macrovascular disease. There is good evidence that hyperglycemia is a core contributor to cardiovascular risk in these patients. The United Kingdom Prospective Diabetes Study (UKPDS) revealed that cardiovascular risk rises with increasing HbA_{1c} but at a slower incremental rate than that for microvascular disease, suggesting a more complex etiology to atherosclerosis than for retinopathy [13]. Even people with mild impairment of fasting plasma glucose level may have excess risk [14]. The Honolulu Heart Program showed during 23 years of follow-up that impaired glucose tolerance doubled the risk of subsequent CVD and suggested that much of the cardiovascular risk accrues before the onset of clinical diabetes [15]. Microalbuminuria is an indicator of the degree of endothelial dysfunction: patients with diabetes and microalbuminuria have a two- to threefold higher risk of cardiovascular events and death than those without this finding but a similar duration of diabetes [16–18].

Case Continued

The patient is informed that, although her clinical examination reveals no evidence of diabetic complications, CVD is a worry because she continues to smoke and is hypertensive as well as diabetic. She is strongly advised to quit smoking and is referred to a local smoking cessation clinic. The importance of tight glucose control is also emphasized. The endocrinologist recommends that the patient begin monitoring her fasting glucose 2 to 3 times per week, with a target level less than 130 mg/dL. The need to intensify therapy with a third oral medication or insulin

should the patient's glycemic indices remain above target and the advantages of initiating treatment with daily aspirin (81 mg) are discussed.

Given the patient's interest in alternative approaches to lowering her cholesterol, she is offered the option of attempting a moderate degree of weight loss (at least 10 lb over the next 6 months) achieved through dietary changes and increased physical activity. She is referred to a nutritionist and a trainer at a local health club. The patient is invited to return in 3 months to check on her progress and to review her glucose records and new laboratory data to be obtained before the next visit.

- **What evidence supports the lifestyle modifications recommended to this patient?**

Weight Reduction

Medical nutrition therapy can result in substantial improvements in glycemia, blood pressure, and lipid levels in individuals with diabetes. However, success with lifestyle intervention requires a coordinated team effort that empowers the patient. Modified diets can be particularly appropriate for those with obesity, CVD, and nephropathy. Hypertensive diabetic patients can reduce their blood pressure through reduction in sodium intake, restriction of alcohol consumption, and reduction of body weight [19].

Weight loss of as little as 5% of body weight can substantially reduce insulin resistance and improve glycemic control. The ICAN (Improving Control with Activity and Nutrition) study followed 147 patients with type 2 diabetes and obesity randomized to lifestyle case management or usual care for 12 months. The lifestyle program (at a cost of $350/person) included a dietician referral and individual/group education. The intervention group had greater weight loss (3 kg), significantly greater reduction in waist circumference, and lower use of oral hypoglycemic agents when compared with usual care [20]. Similarly, a 1-year dietary and exercise intervention on newly diagnosed patients with type 2 diabetes in Finland resulted in a better metabolic control and a moderate reduction in cardiovascular risk factors as compared with the conventional treatment group. Weight reduction and a reduced use of saturated fats appeared to be the main determinants of successful treatment results [21]. The 1-year results of the Look AHEAD trial suggest that intensive lifestyle interventions result in clinically significant weight loss in people with type 2 diabetes, with improved HbA_{1c}, lipid profile, and urine albumin to creatinine ratio and reduced dependency on mediations [22]. A multidisciplinary approach in a weight control center utilizing the expertise of dietician, exercise physiologist, and behavioral therapist would promote implementation of healthy lifestyle behavior and supplement pharmacologic and surgical approaches to weight loss.

Pharmacologic approaches to weight loss generally are not routinely recommended. Rimonabant, a selective cannabinoid receptor blocker shown to reduce body weight and improve cardiometabolic risk factors in overweight and obese patients [23,24], was evaluated in overweight/obese patients with type 2 diabetes who were treated with metformin or a sulfonylurea was studied; after 1 year of treatment with 20 mg of rimonabant, patients had lost a mean of 2.9 kg more than the placebo group, and HbA_{1c} reductions were associated with that weight loss [25]. However, dropout was high, and concerns have been raised about the psychiatric effects of the drug. The U.S. Food and Drug Administration elected not to approve the drug in mid-2007. Other drugs (eg, sibutramine, orlistat) have been investigated in patients with diabetes; however, sibutramine is associated with increases in systolic blood pressure [26], and orlistat (now available over the counter) is not generally well tolerated [27].

According to the National Institutes of Health consensus panel, obese individuals are candidates for weight loss surgery if medical therapy has failed and if they have a BMI of 40 kg/m^2 or greater or a BMI of 35 kg/m^2 or greater with comorbid conditions [28]. The laparoscopic silicone gastric banding procedure and gastric restriction combined with diversion (ie, the Roux-en-Y gastric bypass) are commonly used for inducing weight loss. Most perioperative morbidity occurs from wound infection and cardiopulmonary dysfunction; however, with the emergence of laparoscopic techniques, the mortality rate is now less than 1% [29]. Sustained weight loss through bariatric surgical intervention is associated both with prevention of progression of impaired glucose tolerance and the clinical remission of early type 2 diabetes. In the Swedish Obese Subjects study, bariatric surgery appears to be a viable option for the treatment of severe obesity, resulting in long-term weight loss and graded reduction in the incidence of diabetes following surgery. However, no differences were noted for recovery from hypercholesterolemia in both groups [30].

Exercise

Physical inactivity is a significant risk factor for cardiovascular events in both men and women. In diabetic women, physical inactivity (activity < 1 hour/week) is associated with a doubling of cardiovascular event rates when compared with exercise for 7 hours per week [31]. Men with diabetes share similar risks: low cardiorespiratory fitness increased overall mortality by a factor of 2.9 when compared with moderately or highly fit counterparts [32].

Physical activity continues to be a fundamental form of diabetes management. Exercise influences several aspects

of diabetes, including blood glucose concentrations, insulin action, blood pressure, and lipid concentrations, and contributes to successful weight loss. While exercise produces many benefits, patients should be thoughtful when engaging in a new exercise program. Rarely, exercise can precipitate a cardiac symptom or event, and autonomic neuropathy may predispose patients to exercise-induced arrhythmias. Clinicians may prefer to refer patients planning an exercise program of moderate intensity or greater for evaluation with exercise treadmill testing. During exercise, hyperglycemia can result from excess hepatic glucose output, and ketogenesis can ensue. In contrast, hypoglycemia can result from excess glucose uptake due to either increased insulin concentrations, enhanced insulin action, or impaired carbohydrate absorption during exercise; consequently, insulin doses should be reduced prior to exercise, although some insulin is typically still needed. Blood glucose monitoring before and after exercise is particularly important for those with hypoglycemia unawareness. Appropriate foot care and shoe selection can protect diabetics from developing podiatric complications as a result of their activity.

For patients with diabetes, the overall benefits of exercise are significant. A recent study examining multiple healthy lifestyle habits, including avoidance of smoking, engaging in adequate leisure-time physical activity and consuming 5 or more portions of fruits and vegetables per day, was associated with significantly better quality of life among diabetics [33]. Identifying and preventing potential problems can mitigate complications and promote this valuable approach to healthy living.

Smoking Cessation

Smoking is likely to have at least as detrimental effect on cardiovascular health in patients with diabetes as it does in those without diabetes. Smoking is an independent risk factor for MI, stroke, and all-cause mortality in patients with type 2 diabetes [34]. Diabetic smokers are also at higher risk for accelerated microvascular disease. Data show that cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in patients with type 1 [35] and type 2 [36] diabetes, and smoking increases urine albumin excretion in these patients despite improved blood pressure control and pharmacologic inhibition of the angiotensin-converting enzyme (ACE).

Smoking cessation programs reduces tobacco use and are cost-effective [37]. Furthermore, the risks of macrovascular disease can be reduced by quitting [38], with significant societal cost savings. The most effective smoking cessation programs unite physician and patient, with scheduled follow-ups to review progress and provide support [39]. Discussing reasons for smoking triggers and preferred quit strategy can be useful in negotiating a quit date.

- **What is the evidence in support of aspirin for cardiovascular risk reduction?**

Evidence from controlled clinical trials supports the routine use of enteric-coated aspirin, 81 to 325 mg/day, as a primary and a secondary prevention strategy in adults aged older than 30 with diabetes. The Primary Prevention Project evaluated the effect of low-dose aspirin (100 mg/day) on subsequent cardiovascular events in 4495 individuals with at least 1 of the following risk factors: hypertension, hypercholesterolemia, diabetes, obesity, a family history of premature MI, or being elderly. After a mean follow-up of 3.6 years, aspirin was found to significantly lower the frequency of cardiovascular death (from 1.4%–0.8%) and total cardiovascular events (from 8.2%–6.3%) [40].

The Physician's Health Study, which randomized 22,701 physicians to aspirin or placebo, contained a subgroup of 533 diabetic doctors. After 5 years, 325 mg of aspirin daily reduced the risk of acute MI from 10% to 4% [41]. The Hypertension Optimal Treatment (HOT) trial also demonstrated benefit to post-MI aspirin administration, a benefit that was also seen in their subgroup of 1501 diabetics [42]. Similarly, in the Early Treatment of Diabetic Retinopathy study, aspirin produced a 28% reduction in MIs over 5 years [43].

Retrospective analysis of the diabetic subgroup in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study showed that of the 3866 diabetic patients randomized, 15.6% of those in the clopidogrel arm and 17.7% of those in the aspirin arm had the composite vascular primary endpoint [44]. Clopidogrel appears to be an effective antiplatelet agent for secondary prevention in patients with diabetes, although aspirin is more cost-effective.

- **What evidence supports the goal of tight glycemic control to reduce cardiovascular risk?**

Glycemic Control

Chronic hyperglycemia is associated with a higher cardiovascular event rate, and evidence supports the assertion that reducing glucose levels reduces the risk of developing diabetes-specific complications. The now classic Diabetes Control and Complications Trial (DCCT) and UKPDS studies examined the effect of glucose-lowering on micro- and macrovascular outcomes in patients with type 1 and type 2 diabetes, respectively.

In the DCCT, 1441 type 1 diabetic patients were randomized to conventional or intensive diabetes management and followed for a mean of 6.5 years. Intensive management tar-

geted an HbA_{1c} of 6%. The patients were free of documented CVD, obesity, hypertension, and hypercholesterolemia. Although major macrovascular events were halved in the intensive group (23 vs. 40 events), the difference did not reach statistical significance [45]. Those years of lower glucose levels were ultimately shown to be associated with significant cardiovascular risk reduction, as illustrated by the study's follow-up trial, the Epidemiology of Diabetes Interventions and Complications. Intensive treatment during the DCCT trial was ultimately associated with a 57% lower long-term cardiovascular risk [46]. The beneficial effect of lower glucose levels was reinforced by the finding that coronary artery calcification, an index of atherosclerosis measured by computed tomography, was found to be significantly lower in the intensive therapy group [47].

Although less well proven, the beneficial effect of lowering glucose is likely to be similar in type 2 diabetes. The UKPDS recruited 3867 subjects with type 2 diabetes suboptimally controlled on diet alone and randomized them to conventional treatment (diet unless fasting glucose > 270 mg/dL; $n = 1138$), or intensive treatment with a sulfonylurea ($n = 1573$) or insulin ($n = 1156$) [48]. Another group of 1704 overweight patients (> 120% ideal) were randomized to diet, metformin, sulfonylurea, or insulin [49]. Despite improved HbA_{1c} and microvascular endpoints in the intensively treated patients, the rates of stroke and amputation did not quite reach statistical significance.

- **Do diabetes medications vary in their effect on CVD risk?**

Metformin

Metformin reduces blood glucose levels by reducing hepatic glucose production and improving insulin sensitivity in patients with diabetes. Independent of its glycemic effect, metformin lowers total cholesterol, LDL cholesterol, and particularly triglycerides, but has no effect on HDL cholesterol [50]. Metformin has proven clinical benefit for cardiovascular risk reduction in patients with diabetes and has emerged as a first-line drug for the treatment of type 2 diabetes [51]. In the UKPDS, overweight patients given metformin had fewer atherosclerotic complications, with a particular decrement in MI rates. Results were better for metformin than for sulfonylurea or insulin. With intensive therapy (target glucose, 108 mg/dL), metformin reduced the MI rate by 39% ($P = 0.01$), while sulfonylurea or insulin use was associated with a nonsignificant risk reduction of 21% [49]. Although increasing evidence exists regarding the safety of metformin and the extremely low risk of lactic acidosis (< 8 cases/100,000 patient-years) [52], metformin should nevertheless be avoided in patients with renal, hepatic, pulmonary, or heart failure.

Sulfonylureas

There is a theoretical reason why sulfonylureas may have an adverse effect on diabetic patients with epicardial coronary disease. Sulfonylureas act by inhibiting potassium channels, which are present not only in the pancreatic beta cells but also in the heart and vascular smooth muscle [53]. This class of medications has been shown to prevent cardiac preconditioning, the ability of the heart to recover more quickly after repeated ischemic insults [54]. The UKPDS is often cited in defense of the safety of these agents, as glibenclamide was associated with a reduction in MI rates, which was almost statistically significant ($P = 0.056$). Sulfonylureas, like insulin, increase the risk of weight gain and hypoglycemia. These drugs remain second-line agents for treatment of type 2 diabetes; their combination with metformin is synergistic.

Thiazolidinediones

Thiazolidinediones (TZDs) improve insulin sensitivity and glycemic control and might preserve insulin secretion and beta cell health in patients with type 2 diabetes [55]. These drugs activate peroxisome proliferator-activated receptor-γ (PPAR-γ), which is involved in the process of atherosclerosis, and its modulation for cardioprotection is an active area of investigation. Some beneficial effects attributed to TZDs include a decrease in blood pressure, improvement of fibrinolysis, correction of diabetic dyslipidemia, a decrease in free fatty acid levels, a reduction in inflammatory markers, and a decrease in carotid artery intimal thickness [56,57]. TZDs increase LDL cholesterol levels, although this effect may be offset by favorable changes in LDL particle size and susceptibility to oxidation [58]. In the PROactive study, addition of 45 mg of pioglitazone to other glucose-lowering drugs reduced certain primary outcome measures (all-cause mortality, MI, and stroke) by 16% in patients with type 2 diabetes [57]. However, this study used a higher dose of pioglitazone and excluded patients with New York Heart Association class II congestive heart failure [59].

The DREAM trial was designed to assess prospectively whether rosiglitazone can reduce the frequency of diabetes in individuals with impaired glucose tolerance, impaired fasting glucose, or both. More than 5000 adults with impaired glucose handling but no previous CVD were randomly assigned to receive 8 mg of rosiglitazone or placebo and were followed for 3 years. Rosiglitazone reduced the incidence of new diabetes by 60% and significantly increased the likelihood of regression to normoglycemia [60]. Although frequently associated with an increased risk of heart failure, a recent meta-analysis of prior studies raised concerns regarding the cardiovascular safety of rosiglitazone [61]. This

controversy lead to the early release of an unscheduled interim analysis from the RECORD study, an open-label study that was designed to track cardiovascular events among patients taking rosiglitazone. The interim report was underpowered to detect a significant difference in cardiovascular outcomes, and results are therefore inconclusive. Many clinicians have opted not to prescribe rosiglitazone when alternatives exist; clinicians must weigh the benefits and risks of treatment with rosiglitazone to determine whether to continue the drug [62].

Incretin Mimetics and DPP-4 Inhibitors

Glucagon-like peptide 1 (GLP-1) stimulates postprandial insulin release; however, it is rapidly degraded by the activity of dipeptidyl peptidase-4 (DPP-4). Exenatide and liraglutide are synthetic GLP-1 agonists and have demonstrated glycemic efficacy (HbA_{1c} reductions of 0.7%–2%) associated with mild weight loss; nausea is frequent and can be problematic [63]. Orally administered DPP-4 inhibitors vildagliptin (given twice daily) and sitagliptin (given once daily) have also shown consistent but moderate improvements in the glycemic profile of type 2 diabetic patients [64–66]. These drugs are weight-neutral. It remains unclear whether these expensive drugs will be associated with improved cardiovascular outcomes.

Insulin

Insulin remains the most efficacious method of improving glycemic control. However, insulin exposes the user to a risk of hypoglycemia and induces weight gain. Individuals receiving intensive insulin management as part of the UKPDS gained an average of 8.8 lb; 2.3% of the patients had a severe hypoglycemic event in each year [48]. Nevertheless, intensive insulin therapy has a positive effect on lipoproteins, lowering triglyceride, LDL, and total cholesterol levels [67]. The independent cardiovascular benefits of insulin have not been convincingly demonstrated [48]. In the UKPDS study, the risk of MI in the conventional and intensively treated arms was 17.4 and 14.7 events/1000 patient-years, respectively ($P = 0.052$).

The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial was a secondary prevention study that demonstrated a 30% mortality reduction in 620 Swedish patients randomized to placebo or insulin-glucose infusion followed by at least 3 months of multiple daily insulin injections [68]. It is unclear whether the effect was due to the immediate insulin-glucose infusion or the longer-term improvements in glycemic control resulting from ongoing insulin administration.

Newer, long-acting insulin analogs such as insulin glargine and insulin detemir can be safely introduced to patients on oral hypoglycemic agents. A home titration schedule starting at 10 units daily and increasing weekly to a target of a fasting glucose of no more than 100 mg/dL is highly efficacious for reducing HbA_{1c} to 7% with minimal risk of hypoglycemia [69,70]. The recently released results from the ACCORD study suggest caution in aiming for excessively low glucose values.

- **What evidence supports the goal of tight blood pressure control in diabetic patients, and how should it be achieved?**

Blood Pressure Control

Hypertension affects up to 60% of patients with diabetes and rises in prevalence with age and increasing levels of obesity. Hypertension is a major risk factor in the development of both macro- and microvascular complications of diabetes. In type 1 diabetes, the hypertension is often secondary to underlying nephropathy, while hypertension in type 2 diabetes often forms part of the metabolic syndrome. As soon as blood pressure rises above 120/80 mm Hg, cardiovascular risk in diabetic patients appreciates [42], and treatment is recommended when the blood pressure exceeds 130/80 mm Hg [71]. Before starting antihypertensive therapy, patients should be re-examined within 1 month for confirmation, unless the initial diastolic value is greater than 110 mm Hg. Many of these patients require multidrug therapy for control. Many classes of antihypertensives have had demonstrated efficacy in diabetics.

ACE inhibitors and angiotensin receptor blockers (ARBs) have been demonstrated to reduce blood pressure, reduce cardiovascular events [72], and slow the progression of nephropathy [73–80]. The Heart Outcomes Protection Evaluation (HOPE) trial reported on 3577 people with diabetes out of 9541 people aged at least 55 years who also had another vascular risk factor such as smoking, hypertension, or microalbuminuria. The trial found that 10 mg of ramipril versus placebo over 4.5 years reduced cardiovascular mortality by 37%, MI by 22%, and stroke by 33% among individuals with diabetes [76]. A subgroup from the HOPE study underwent carotid ultrasound to evaluate carotid intimal medial thickness. Those treated with ramipril had a 37% reduction in the rate of thickening, reflecting healthier endothelial function [81]. The relative benefit of ramipril was present in all subgroups regardless of hypertensive status, microalbuminuria, type of diabetes, and nature of diabetes treatment (diet, oral agents, or insulin). The mean reduction in blood pressure with treatment (3/2 mm Hg) appeared to be too small to independently account for the risk reductions achieved. Patient with creatinine concentrations greater than 1.4 mg/dL had an even greater benefit than those with more normal renal function. Although widely and appropriately recommended for managing hypertension in patients with diabetes, it is

worth recognizing that 3 studies—QUIET, SCAT, and PART-2 [82–84]—failed to show cardiovascular benefits to ACE inhibitor use.

Diuretics and β blockers have proven efficacy in blood pressure control. Thiazide diuretics and β blockers are both associated with mild increases in serum glucose. Their benefits outweigh this mild effect, and their use is generally recommended to reach target blood pressure goals [85,86]. Atenolol has been demonstrated to have the same cardiovascular benefit when compared with captopril in diabetics [87], and β blockers are known to significantly reduce cardiovascular events in nondiabetic patients with ischemic heart disease. Additionally, the UKPDS found no difference in outcome between those on ACE inhibitors and those treated with β blockers.

Concerns for metabolic complications and a possible increase in cardiovascular risk as a result of high-dose diuretics in hypertensive diabetics can likely be assuaged by using low-dose therapy, such as 12.5 to 25 mg of hydrochlorothiazide per day. Lowering blood pressure with thiazides can reduce cardiovascular risk: the Systolic Hypertension in Elderly Patients (SHEP) trial demonstrated that a diuretic (chlorthalidone) improved cardiovascular outcomes, providing twice as much benefit to diabetic patients as nondiabetics.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was stopped early after interim analysis revealed a substantial benefit of diuretics over α-blocking agents [88]. Calcium channel blockers appear to be inferior to ACE inhibitors in cardiovascular protection [89] but are often good choices as additional therapy given their efficacy for controlling blood pressure, particularly in African-American patients.

As a result of these and other studies, major professional organizations recommend ACE inhibitors or ARBs with or without thiazide diuretics as first-line therapy for patients with type 2 diabetes. β Blockers and calcium-channel blockers tend to be used as third-line drugs, with additional therapy individualized.

- **What evidence supports the use of lipid-lowering therapy to reduce cardiovascular risk, and what strategies should be used in diabetic patients?**

Lipid Management Goals

The typical lipid profile seen in patients with type 2 diabetes—abnormally low levels of HDL cholesterol, significantly elevated triglyceride levels, and abnormally small, dense, and atherogenic LDL cholesterol—represents a significant risk factor for coronary heart disease (CHD) [90–93]. Generally speaking, LDL levels are not higher or more often elevated in diabetic patients than in nondiabetic individuals, but the presence of abnormally high LDL levels should be regarded as an additional risk factor to address in diabetic patients.

Table 2. Management of Diabetic Dyslipidemia

Treatment choices for each lipid target given in order of priority:
Low-density lipoprotein (target, < 100 mg/dL)
Lifestyle modification
Statin
Ezetimibe
Fibrate
High-density lipoprotein (target, > 40/45 mg/dL for men/women)
Lifestyle modification
Fibrate
Niacin
Triglycerides (target, < 150 mg/dL)
Lifestyle modification
Glycemic control
Fibrate
Niacin

The NCEP Adult Treatment Panel III (ATP III) designation of diabetes as a "CHD risk equivalent" (ie, carrying a risk for major coronary events equivalent to established CHD), justifies aggressive lipid lowering in patients with diabetes, as if they already have CVD [94]. The ATP III recommended that pharmacologic therapy be initiated in diabetic patients whose LDL levels are 130 mg/dL or greater and that patients be treated to target LDL levels less than 100 mg/dL. A goal of 70 mg/dL or lower is an appropriate target for patients at especially high risk. The ADA recommends the additional goals of raising HDL levels above 40 mg/dL in men and 45 mg/dL in women and lowering triglycerides below 150 mg/dL (**Table 2**).

Statins

Though an elevated LDL is not characteristic of diabetes, current guidelines for managing diabetic dyslipidemia typically target LDL cholesterol, as the strongest evidence in support of lipid-lowering therapy for diabetic patients comes from studies showing the benefit of HMG-CoA reductase inhibitors (statins). Statin therapy has proven to be particularly useful in treating dyslipidemia and has resulted in significant reductions in coronary events in several large primary and secondary trials. A few of these early statin trials included a relatively small number of patients with diabetes.

The most important trial to date examining the relationship between CVD, diabetes, and statins is the Collaborative Diabetes Study (CARDS) [95]. Atorvastatin (10 mg/day) was given as primary prevention to 2838 patients with type 2

diabetes and 1 other risk factor (hypertension, albuminuria, retinopathy, or current smoking). The LDL level at recruitment was required to be less than 160 mg/dL. After a mean follow-up of 3.9 years, death rates among those on atorvastatin were 27% lower; in addition, acute coronary event rates were reduced by 36%, revascularizations by 31%, and stroke rates by 48%. Patients with an LDL level less than 100 mg/dL had the same magnitude of benefit as those with a higher LDL. This result has challenged the recommendation that statins be introduced to patients with diabetes only when the LDL is above a threshold.

The Heart Protection Study recruited 20,536 individuals on the basis of having established coronary artery disease (65%), diabetes (19%), peripheral vascular disease (13%), or a history of cerebrovascular disease (9%) and randomly assigned them to simvastatin (40 mg/day) or placebo [96]. A relative risk reduction of 25% was observed for coronary and cerebrovascular events, whether the diabetic subjects already had coronary disease or not, confirming the role of statins for primary prevention of cardiac events [96].

Two negative studies are worthy of note. In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT–LLA) trial [97], investigators randomized 2532 subjects with diabetes, hypertension, but without known CVD to atorvastatin (10 mg/day) or placebo. Atorvastatin did not reduce the risk of nonfatal MI and coronary heart disease death in patients with diabetes and hypertension despite a reduction of 40 to 50 mg/dL in LDL cholesterol (comparable with that observed in the CARDS trial). The lack of demonstrable effect may have been confounded by a noted increase in statin utilization in the placebo group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT–LLT) was nonblinded, and pravastatin (40 mg/day) also did not reduce incidence of nonfatal MI and CHD death among 3638 patients with diabetes; however, only a modest 15 to 23 mg/dL reduction in LDL cholesterol concentrations was achieved in the treated versus the usual care group [98].

The role of statins for secondary prevention of CVD is more clearly established. Although large trials of patients with CVD were recruited for these landmark studies, they contained relatively small numbers of patients with diabetes; nevertheless, the large effect size noted is worthy of notice. The landmark Scandinavian Simvastatin Survival Study (4S) included 202 patients with diabetes with a previous MI or angina and a mean LDL cholesterol level of 187 mg/dL [99]. The study followed patients for a median of 5.4 years and tracked mortality, coronary death, acute coronary syndromes, or coronary revascularization. In the 4S, individuals with diabetes benefited from the medication as much as those without diabetes. Over the course of the trial, in the simvastatin-treated diabetic patients, the mean changes from baseline in total, LDL, and HDL cholesterol and triglycerides were –27%, –36%, +7%, and –11%, respectively. As a result, mortality was reduced by 43%, major coronary events by 55%, and any atherosclerotic event by 37%.

The Cholesterol and Recurrent Events (CARE) trial evaluated the effect of pravastatin on 586 diabetic patients with a history of MI and a mean LDL cholesterol level of 136 mg/dL [100]. In diabetic patients randomized to treatment, LDL cholesterol was reduced to a mean of 98 mg/dL and the recurrent coronary event rate (coronary death, MI, bypass grafting, or angioplasty) was reduced 25% over 5 years; however, the event rates in treated diabetic patients remained higher than event rates in nondiabetic patients, whether randomized to treatment or not.

Fibrates

Epidemiologic evidence links the combined abnormality of elevated triglyceride levels and low HDL levels with adverse cardiovascular outcomes, independent of LDL cholesterol concentrations [101]. Recent randomized controlled trials, such as the Veterans Affairs HDL Intervention Trial (VA-HIT), have demonstrated a reduction in cardiovascular events using fibrate therapy to lower triglyceride levels and raise HDL levels [102,103]. The VA-HIT enrolled 2531 patients—25% with established diabetes and 6% with newly diagnosed diabetes by fasting glucose—and randomized them to gemfibrozil or placebo. The criteria for entry were a LDL level of 140 mg/dL or less, a triglyceride level less than 300 mg/dL, and an HDL level of 40 mg/dL or less. At follow-up, the HDL level was 6% higher and the mean triglyceride level was 31% lower in the treatment group. Compared with placebo, treatment resulted in an 18% reduction in major cardiovascular events in nondiabetic patients and a 32% reduction in diabetic patients, with the greatest rate decreases occurring in stroke and coronary death. Of note, the mean baseline LDL of 108 mg/dL did not change throughout the study; therefore, LDL cholesterol did not determine coronary event rates. It is likely that the known PPAR-α effect of gemfibrozil contributed by improving endothelial function. In the Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) study, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. The treatment benefit may have been masked by the higher use of statins in the placebo group [104]. Another observation in the fenofibrate group is the increase in plasma homocysteine levels, which could partly explain higher number of venous thrombotic events, especially in patients with preexisting atherosclerotic plaques [105].

Fibrates can be useful alone or in combination with statins. The combination of a statin and fenofibrate has been shown to be clinically useful in patients with diabetes [106]. When using combination therapy, many practitioners

choose fluvastatin or pravastatin, as these agents are not metabolized by cytochrome P450 3A4, are hydrophilic, and are only 50% protein-bound—all factors that reduce adverse drug interactive effects such as rhabdomyolysis, a known risk of combining statins with fibrates [107]. Furthermore, fenofibrate appears to be safer in combination with statins than gemfibrozil [108].

Niacin

Niacin treatment can increase HDL cholesterol and reduce triglyceride levels; however, it has also been associated with increased insulin resistance and consequent hyperglycemia. A randomized controlled trial of 148 patients with diabetes found that niacin did not cause any deterioration of glycemic control until the dose of extended-release niacin exceeded 1000 mg [109]. In the Arterial Disease Multiple Intervention Trial (ADMIT), which evaluated immediate-release niacin in the treatment of dyslipidemia associated with diabetes and peripheral vascular disease, 125 patients with diabetes were randomized to receive crystalline niacin 3 g/day (or the maximally tolerated dose) or placebo [110]. Niacin use significantly increased HDL by 29% and decreased triglycerides by 23% and LDL by 8% over 60 weeks. However, insulin use increased in 13% of those on niacin versus 4% of those on placebo ($P = 0.09$) [110], consistent with prior recognition of the hyperglycemic effects of niacin.

Niacin is distinct from other lipid-lowering agents in that it has a broad spectrum of beneficial effects on lipids and atherogenic lipoprotein subfraction levels [111]. Extended-release niacin is associated with a reduction in the more common adverse effects of flushing and diarrhea seen with crystalline niacin, and the beneficial effects on the lipid profile are maintained [112]. Although myositis can result from combinations of niacin and statins, a number of studies have demonstrated the relative safety and effectiveness of this combination approach [113]. Nevertheless, many patients appear to find the side effects uncomfortable, and alternative agents are available. As a result, niacin use remains limited among the diabetic population.

Polyunsaturated Fatty Acids

A highly purified formulation of omega-3 polyunsaturated fatty acids (eicosapentaenoic acid, 465 mg, and docosahexaenoic acid, 375 mg) in a 1-g capsule along with 4 mg of vitamin E has been formulated [114]. In combination with statins, this formulation (Omacor, Reliant Pharmaceuticals, Liberty Corner, NJ) has been shown to effectively reduce plasma triglycerides and also increase the potentially less atherogenic form of LDL cholesterol while decreasing the small dense and atherogenic LDL particles. In patients with a history of MI, the formulation in combination with a statin has been associated with a 14% lower risk of death, nonfatal MI, and stroke. Four capsules of the formulation must be administered daily for clinical effect [115].

Ezetimibe

Ezetimibe selectively inhibits intestinal absorption of dietary cholesterol. The agent is typically used in patients on high-dose statin as additive therapy. An industry-sponsored Australian trial studied the effect of adding 10 mg daily of ezetimibe or placebo to 195 diabetic patients already taking a statin [116]. The combination of agents was significantly more effective than statin alone at lowering plasma levels of LDL (mean reduction, 27%), total cholesterol (18%), apolipoprotein B (20%), and triglycerides (16%), and 84% of the diabetic patients reached their LDL goal within 8 weeks. Ezetimibe appears to be safe for use in diabetic patients [116,117], but large-scale trials have not been reported, and it remains unclear whether its use is associated with the cardiovascular benefit that would be expected from this degree of lipid improvement. Indeed the recently released results from the ENHANCE study suggests that ezetimibe treatment is not associated with the regression of atherosclerosis as might have been expected [118].

Torcetrapib

Torcetrapib increases HDL cholesterol while reducing LDL cholesterol and apolipoprotein B by the inhibition of cholesterol ester transfer protein. Despite success in phase 2 trials [119], a 15,000-patient phase 3 clinical trial (ILLUMINATE) was abruptly terminated as patients receiving this drug had higher risks of heart failure, angina, and cardiovascular mortality.

Case Conclusion

The patient returns 3 months later. She has successfully quit smoking and has remained tobacco-free for 8 weeks. The accompanying weight gain has been frustrating, although she is trying to adhere to the recommended dietary changes. Exercise has been sporadic.

The patient's blood glucose monitor shows levels averaging slightly above target, and her HbA_{1c} is minimally reduced at 7.3%. Blood pressure is also largely unchanged (134/84 mm Hg). LDL and triglyceride levels are decreased but remain above target (132 mg/dL and 180 mg/dL, respectively).

- **What are appropriate interventions at this time?**

Given this patient's limited glycemic improvement with lifestyle interventions while on maximal metformin and glipizide, an appropriate next step would be to replace the

sulfonylurea with a once-daily long-acting insulin regimen started at night, with a home titration algorithm as in the Treat to Target study [69]. In addition, her ramipril dose should be titrated or a thiazide diuretic treatment could be initiated. Finally, she should clearly receive a statin drug to lower LDL cholesterol, and aspirin. Her triglyceride level would be expected to decrease as glycemic control improves.

CONCLUSION

As the leading cause of death among patients with diabetes, CVD should be a primary concern for patients with type 2 diabetes and the physicians who care for them. Clinicians need to be sensitive to the challenges these patients face in making therapeutic lifestyle changes and adept at navigating the polypharmacy that follows from targeting multiple CVD risk factors.

Most patients with diabetes will require at least 1 oral hypoglycemic drug, and almost all will ultimately require insulin. Until further data emerge, the most appropriate initial choices remain metformin and a sulfonylurea, moving to a combination of metformin and a long-acting insulin when glycemic control is suboptimal on maximal dose therapy.

Achieving a systolic blood pressure less than 130 mm Hg in patients with diabetes remains challenging. Almost all patients should be treated with an ACE inhibitor or ARB. Rational additive treatment includes a thiazide diuretic and β blocker as needed. Most patients will require at least 3 drugs for control. In the absence of contraindications, 81 mg of aspirin should be given to all patients with diabetes who are aged 40 years or older; clopidogrel is an alternative.

For patients with diabetes whose lipid levels are not at target range, nonpharmacologic interventions (diet and exercise) remain first-line therapies. Lowering LDL cholesterol is the first priority in treating diabetic dyslipidemia. Statins are the agents of first choice, followed by fibrates or ezetimibe. For elevated triglyceride levels, hyperglycemia must be controlled first. For other dyslipidemia, fibrates are slightly more effective than niacin in lowering triglyceride levels, but niacin increases HDL levels appreciably more than fibrates.

As confirmed by the STENO-2 study, an integrated approach to diabetes management can halve the rate of cardiovascular events [120]. Online tools [121], templates, and close follow-up can help clinicians avoid the inertia that often accompanies the management of complex patients [122], such as those with diabetes. Although physicians are empowered by these advances, patients are unlikely to perceive the benefits unless we continue to nurture the patient-clinician relationship and build on the trust our patients place in us. These remain fundamental cornerstones in helping protect our patients from the long-term effects of their disease.

Corresponding author: Graham T. McMahon, MD, MMSc, Div. of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Ave., RF-291, Boston, MA 02115, gmcmahon@partners.org.

Financial disclosures: None.

References

1. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280–99.
2. Berry JD, Dyer A, Carnethon M, et al. Association of traditional risk factors with cardiovascular death across 0 to 10, 10 to 20, and > 20 years follow-up in men and women. Am J Cardiol 2008;101:89–94.
3. Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care 1998; 21:69–75.
4. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. N Engl J Med 1996;335:217–25.
5. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773–8.
6. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426–32.
7. American Diabetes Association. Standards of medical care in diabetes–2008. Diabetes Care 2008;31 Suppl 1:S12–54.
8. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883–92.
9. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
10. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227–39.
11. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–44.
12. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
13. Opara JU, Levine JH. The deadly quartet—the insulin resistance syndrome. South Med J 1997;90:1162–8.

14. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999; 22:233–40.
15. Rodriguez BL, Lau N, Burchfiel CM, et al. Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. Diabetes Care 1999;22:1262–5.
16. Messent JW, Elliott TG, Hill RD, et al. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. Kidney Int 1992;41:836–9.
17. Geluk CA, Tio RA, Tijssen JG, et al. Clinical characteristics, cardiac events and coronary angiographic findings in the prospective PREVEND cohort: an observational study. Neth Heart J 2007;15:133–41.
18. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6.
19. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117–24.
20. Wolf AM, Conaway MR, Crowther JQ, et al. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. Diabetes Care 2004;27:1570–6.
21. Uusitupa MI. Early lifestyle intervention in patients with non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Ann Med 1996;28:445–9.
22. Pi-Sunyer X, Blackburn G, Brancati FL, et al; Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the LOOK AHEAD trial. Diabetes Care 2007;30:1374–83.
23. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353:2121–34.
24. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006;295:761–75.
25. Hollander P. Endocannabinoid blockade for improving glycemic control and lipids in patients with type 2 diabetes mellitus. Am J Med 2007;120(2 Suppl 1):S18–28.
26. Fujioka K, Seaton TB, Rowe E, et al. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. Diabetes Obes Metab 2000;2:175–87.
27. Berne C. A randomized study of orlistat in combination with a weight management programme in obese patients with type 2 diabetes treated with metformin. Diabet Med 2005;22:612–8.
28. Burguera B, Agusti A, Arner P, et al. Critical assessment of the current guidelines for the management and treatment of morbidly obese patients. J Endocrinol Invest 2007;30:844–52.
29. Choban PS, Jackson B, Poplawski S, Bistolarides P. Bariatric surgery for morbidly obesity: why, who, when, how, where, and then what? Cleve Clin J Med 2002;69:897–903.
30. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93.
31. Hu FB, Stampfer MJ, Solomon C, et al. Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med 2001;134:96–105.
32. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000;132:605–11.
33. Li C, Ford ES, Mokdad AH, et al. Clustering of multiple healthy lifestyle habits and health-related quality of life among U.S. adults with diabetes. Diabetes Care 2007;30:1770–6.
34. Mikhailidis DP, Papadakis JA, Ganotakis ES. Smoking, diabetes and hyperlipidaemia. J R Soc Health 1998;118:91–3.
35. Sawicki PT, Didjurgeit U, Muhlhauser I, et al. Smoking is associated with progression of diabetic nephropathy. Diabetes Care 1994;17:126–31.
36. Chuahirun T, Khanna A, Kimball K, Wesson DE. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. Am J Kidney Dis 2003;41:13–21.
37. Fiore M, Bailey W, Cohen S. Smoking cessation: clinical practice guideline number 18. Rockville (MD): U.S. Department of Health and Human Services; 1996.
38. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. Circulation 1997;96:1089–96.
39. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. Diabetes Care 1999;22:1887–98.
40. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet 2001;357:89–95.
41. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321:129–35.
42. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755–62.
43. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA 1992;268:1292–300.
44. Bhatt DL, Marso SP, Hirsch AT, et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol 2002;90:625–8.
45. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75:894–903.
46. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53.
47. Cleary PA, Orchard TJ, Genuth S, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes 2006;55:3556–65.

48. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.
49. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.
50. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995;333: 541–9.
51. Nathan DM. Thiazolidinediones for initial treatment of type 2 diabetes? N Engl J Med 2006;355:2477–80.
52. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2003;163:2594–602.
53. Engler RL, Yellon DM. Sulfonylurea KATP blockade in type II diabetes and preconditioning in cardiovascular disease. Time for reconsideration. Circulation 1996;94:2297–301.
54. Cleveland JC Jr, Meldrum DR, Cain BS, et al. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. Circulation 1997; 96:29–32.
55. Martens FM, Visseren FL, Lemay J,et al. Metabolic and additional vascular effects of thiazolidinediones. Drugs 2002;62: 1463–80.
56. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296: 2572–81.
57. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
58. Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med 2001;134:61–71.
59. Fonseca V, Jawa A, Asnani S. Commentary: the PROactive study—the glass is half full. J Clin Endocrinol Metab 2006; 91:25–7.
60. Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–105.
61. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published erratum appears in N Engl J Med 2007;357:100]. N Engl J Med 2007;356:2457–71.
62. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. N Engl J Med 2007;357:28–38.
63. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–705.
64. Kleppinger EL, Helms K. The role of vildagliptin in the management of type 2 diabetes mellitus. Ann Pharmacother 2007; 41:824–32.
65. Ristic S, Byiers S, Foley J, Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. Diabetes Obes Metab 2005;7:692–8.
66. Herman GA, Stein PP, Thornberry NA, Wagner JA. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: focus on sitagliptin. Clin Pharmacol Ther 2007;81:761–7.
67. Taskinen MR, Kuusi T, Helve E, et al. Insulin therapy induces antiatherogenic changes of serum lipoproteins in noninsulin-dependent diabetes. Arteriosclerosis 1988;8:168–77.
68. Davies MJ, Lawrence IG. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction): theory and practice. Diabetes Obes Metab 2002;4:289–95.
69. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26: 3080–6.
70. Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005;28:254–9.
71. American Diabetes Association. Executive summary: standards of medical care in diabetes—2008. Diabetes Care 2008; 31 Suppl 1:S5–11.
72. Zuanetti G, Latini R, Maggioni AP, et al. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. Circulation 1997;96:4239–45.
73. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. Am J Med 1995;99:497–504.
74. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. The Microalbuminuria Captopril Study Group. Diabetologia 1996;39:587–93.
75. Mathiesen ER, Hommel E, Hansen HP, et al. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 1999;319:24–5.
76. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253–9.
77. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group. Lancet 1997;349:1787–92.
78. Ravid M, Brosh D, Levi Z, et al. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1998;128(12 Pt 1):982–8.
79. Chaturvedi N, Sjolie AK, Stephenson JM, et al. Effect of lisinopril on progression of retinopathy in normotensive people

with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. Lancet 1998;351:28–31.
80. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703–13.
81. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611–6.
82. Cashin-Hemphill L, Holmvang G, Chan RC, et al. Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. QUIET Investigators. QUinapril Ischemic Event Trial. Am J Cardiol 1999;83:43–7.
83. Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). Circulation 2000;102:1748–54.
84. MacMahon S, Sharpe N, Gamble G, et al. Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. PART-2 Collaborative Research Group. Prevention of Atherosclerosis with Ramipril. J Am Coll Cardiol 2000;36: 438–43.
85. Asfaha S, Padwal R. Antihypertensive drugs and incidence of type 2 diabetes: evidence and implications for clinical practice. Curr Hypertens Rep 2005;7:314–22.
86. Gress TW, Nieto FJ, Shahar E, et al. Hypertensive and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 2000; 342:905–12.
87. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998; 317:713–20.
88. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Lancet 2000;355:863–4.
89. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645–52.
90. Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995;75:473–86.
91. Austin MA, Edwards KL. Small, dense low density lipoproteins, the insulin resistance syndrome and noninsulin-dependent diabetes. Curr Opin Lipidol 1996;7:167–71.
92. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 1977;62:707–14.
93. Fontbonne A, Eschwege E, Cambien F, et al. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989;32:300–4.
94. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
95. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.
96. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
97. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
98. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.
99. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20: 614–20.
100. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. Circulation 1998;98:2513–9.
101. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Munster study. Am J Cardiol 1992;70:733–7.
102. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410–8.
103. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597–604.
104. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61.
105. Verges B. Fenofibrate therapy and cardiovascular protection in diabetes: recommendations after FIELD. Curr Opin Lipidol 2006;17:653–8.
106. Athyros VG, Papageorgiou AA, Athyrou VV, et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care 2002;25:1198–202.
107. Corsini A. The safety of HMG-CoA reductase inhibitors in

special populations at high cardiovascular risk. Cardiovasc Drugs Ther 2003;17:265–85.
108. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. Am J Cardiol 2007;99: 3C–18C.
109. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med 2002;162:1568–76.
110. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. JAMA 2000;284:1263–70.
111. Meyers CD, Kamanna VS, Kashyap ML. Niacin therapy in atherosclerosis. Curr Opin Lipidol 2004;15:659–65.
112. Carlson LA. Niaspan, the prolonged release preparation of nicotinic acid (niacin), the broad-spectrum lipid drug. Int J Clin Pract 2004;58:706–13.
113. Asztalos BF. High-density lipoprotein metabolism and progression of atherosclerosis: new insights from the HDL Atherosclerosis Treatment Study. Curr Opin Cardiol 2004;19:385–91.
114. Bays H. Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. Am J Cardiol 2006; 98:71i–6i.
115. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447–55.
116. Simons L, Tonkon M, Masana L, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Curr Med Res Opin 2004;20:1437–45.
117. Stroup JS, Kane MP, Busch RS. The antilipidemic effects of ezetimibe in patients with diabetes. Diabetes Care 2003;26:2958–9.
118. In brief: Zetia and Vytorin: the ENHANCE study. Med Lett Drugs Ther 2008;50:5.
119. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med 2007;356:1304–16.
120. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
121. McMahon GT, Gomes HE, Hickson Hohne S, et al. Web-based care management in patients with poorly controlled diabetes. Diabetes Care 2005;28:1624–9.
122. Perlin JB, Pogach LM. Improving the outcomes of metabolic conditions: managing momentum to overcome clinical inertia. Ann Intern Med 2006;144:525–7.