

Type 2 Diabetes Mellitus Is Associated with Multiple Cardiometabolic Risk Factors

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The risk for cardiovascular disease (CVD) is multifactorial and includes such risk factors as diabetes, hypertension, smoking, and dyslipidemia. Thus, targeting the hyperglycemia in type 2 diabetes mellitus (DM) alone will not eliminate all of the excess cardiovascular risk; rather aggressive treatment is needed for all of the modifiable cardiometabolic risk factors. Therapeutic lifestyle change is considered primary therapy for hyperglycemia in type 2 DM. Currently, however, the focus in treatment is on preventing CVD rather than controlling glucose, lipid, or blood pressure (BP) levels. The American Diabetes Association guidelines identify low-density lipoprotein cholesterol as the first priority of lipid lowering, with optimal level set at <100 mg/dL (2.6 mmol/L). To reach the target BP level of <130/85 mm Hg, >65% of patients with DM and hypertension will require 2 or more different antihypertensive drugs. Strategies that combine thiazolidinediones and statins may have complementary effects on cardiovascular risk-factor profiles in type 2 DM, in addition to controlling glycemia. Despite the range of treatment options available, therapeutic agents that target new steps in the progression of CVD are needed, as patients with type 2 DM remain at increased risk and many do not achieve therapeutic targets with the drugs available. (*Clinical Cornerstone*. 2007;8[3]:53–68) Copyright © 2007 Excerpta Medica, Inc.

Cardiometabolic risk factors by definition predispose patients to cardiovascular disease (CVD) and type 2 diabetes mellitus (DM). These risk factors range from smoking and obesity to elevated glucose levels and hypertension (**Table I**).¹ Patients should undergo treatment not only for their glucose disorders but for all of their cardiovascular risk factors. Because of the relationship between obesity, especially abdominal or central obesity, and other cardiometabolic risk factors, weight loss is critically important if patients are overweight. However, weight loss is often overlooked or not emphasized sufficiently as a treatment option during efforts to control blood glucose, blood pressure (BP), and dyslipidemia in patients with type 2 DM. This paper reviews the magnitude of the risk of CVD in patients with type 2 DM and presents guidelines and treatment strategies for minimizing cardiovascular risk factors in these patients.

CARDIOVASCULAR DISEASE RISK IN TYPE 2 DIABETES MELLITUS

Type 2 DM is an independent risk factor for macrovascular disease and is often accompanied by other CVD risk factors. Patients with type 2 DM have an increased prevalence of lipid abnormalities that contribute to higher rates of CVD.² CVD is the major cause of mortality for individuals with type 2 DM.^{2–4} Adults with type 2 DM have cardiovascular death rates 2 to 4 times higher than those of adults without it.^{3,5} In fact, patients with type 2 DM but no history of myocardial infarction (MI) have as high a risk of dying as patients without type 2 DM who have a history of MI (**Figure 1**).³

Type 2 DM causes microvascular disease. Patients are often diagnosed with type 2 DM 4 to 7 years after the disease process had begun (**Figure 2**), by which time ~20% already exhibit microvascular diabetic complications.⁶ They are also 2 to 5 times more likely to develop

TABLE I. CARDIOMETABOLIC RISK FACTORS.

Cardiometabolic risk describes the cluster of modifiable risk factors or markers that identify individuals at increased risk for cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease) and type 2 diabetes:

- Smoking
- Elevated low-density lipoprotein cholesterol
- Inflammatory markers
- Insulin resistance
- Impaired insulin secretion

Included in the definition of metabolic syndrome:

- Elevated blood pressure
- Abdominal adiposity
- Low level of high-density lipoprotein cholesterol
- Elevated triglycerides
- Elevated blood glucose

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macrovascular disease (ie, CVD) than nondiabetic individuals.⁶ These complications occur as a result of the fact that glycemia is a continuous risk factor for vascular disease with no apparent threshold.⁷

The absolute risk of CVD varies depending on the type of diabetes, age, and the baseline risk in the population. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and the American Heart Association have designated diabetes as a CVD risk equivalent and recommend intensive risk-factor management.^{5,8} The INTERHEART study,⁹ an international, standardized, case-control study of >27,000 individuals from 52 countries, demonstrated that diabetes is a risk factor of equivalent magnitude to hypertension for MI. Indeed, the risk of MI was increased 3.8-, 3.2-, 2.2-, and 2.0-fold for smoking, dyslipidemia, diabetes, and hypertension, respectively.

Moreover, CVD accounts for a large proportion of the health care use attributable to DM.² Chronic complications of DM include several types of CVD, such as ath-

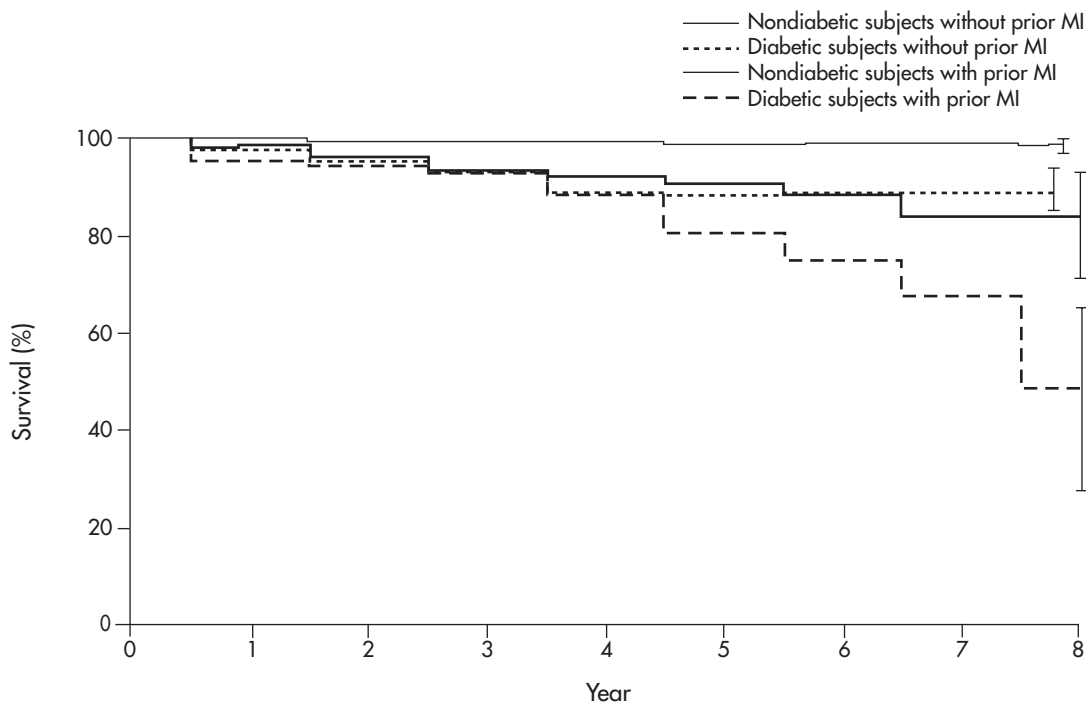


Figure 1. Probability of death from coronary heart disease (CHD) in patients with and without diabetes. Kaplan-Meier estimates of the probability of death from CHD in 1059 patients with type 2 diabetes and 1378 nondiabetic patients with and without a history of myocardial infarction (MI). The vertical bars represent 95% CIs. Reproduced with permission from 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;339:229–234. © Copyright 1998, Massachusetts Medical Society. All rights reserved.

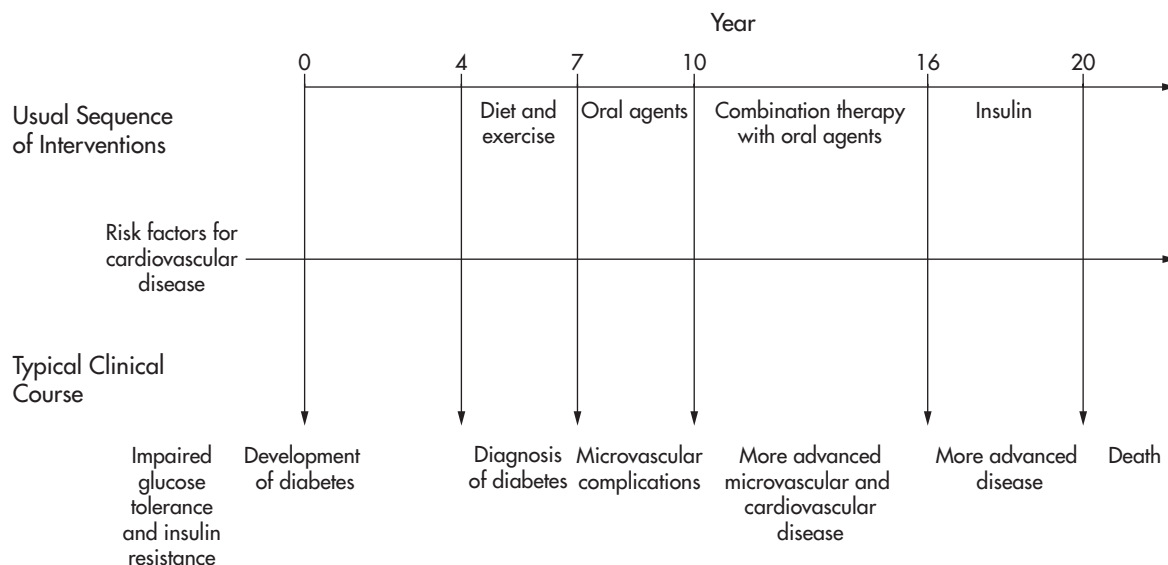


Figure 2. The typical clinical course of type 2 diabetes, including the progression of glycemia and the development of complications, and the usual sequence of interventions. Reproduced with permission from Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med.* 2002;347:1342–1349. © Copyright 2002, Massachusetts Medical Society. All rights reserved.

erosclerotic CVD, cardiomyopathy, heart failure, MI, angina pectoris, stroke, and transient ischemic attack.^{2,10} Patients with type 2 DM have an array of risk factors or markers for CVD (eg, dyslipidemia, elevated levels of inflammatory mediators and coagulation/thrombolytic factors, hypertension) in addition to hyperglycemia, as well as other nontraditional risk factors, many of which are closely associated with insulin resistance.^{11,12} Cardiometabolic risk may remain, however, despite treatment of risk factors,¹³ since patients often do not achieve therapeutic targets for all risk factors.

KEY POINT

Type 2 DM often coexists with other cardiometabolic risk factors such as hypertension and dyslipidemia. Cardiometabolic risk may remain, however, despite treatment of risk factors.

The level of control of cardiovascular risk factors among patients with type 2 DM can be estimated from the Third National Health and Nutrition Examination Survey

(NHANES III, 1988–1994) and NHANES 1999–2000.^{14,15} Less than 10% of patients had good control over all 3 risk factors, including glycosylated hemoglobin (A1C), BP, and total cholesterol levels (**Figure 3**).¹⁴ One reason for suboptimal control is inadequately aggressive treatment of cardiovascular risk factors in patients with type 2 DM because of the perception that a long time will elapse between diagnosis and the development of macrovascular complications.¹⁶ This perception is incorrect, however, as demonstrated in a study of >12,000 patients in the type 2 DM cohort of a prescription database.¹⁶ Age-standardized incidence rates of stroke were compared between the DM cohort and the general population. The risk of stroke was

KEY POINT

One reason for suboptimal treatment of cardiovascular risk factors in patients with type 2 DM is the perception that a long time will elapse between diagnosis and the development of macrovascular complications.

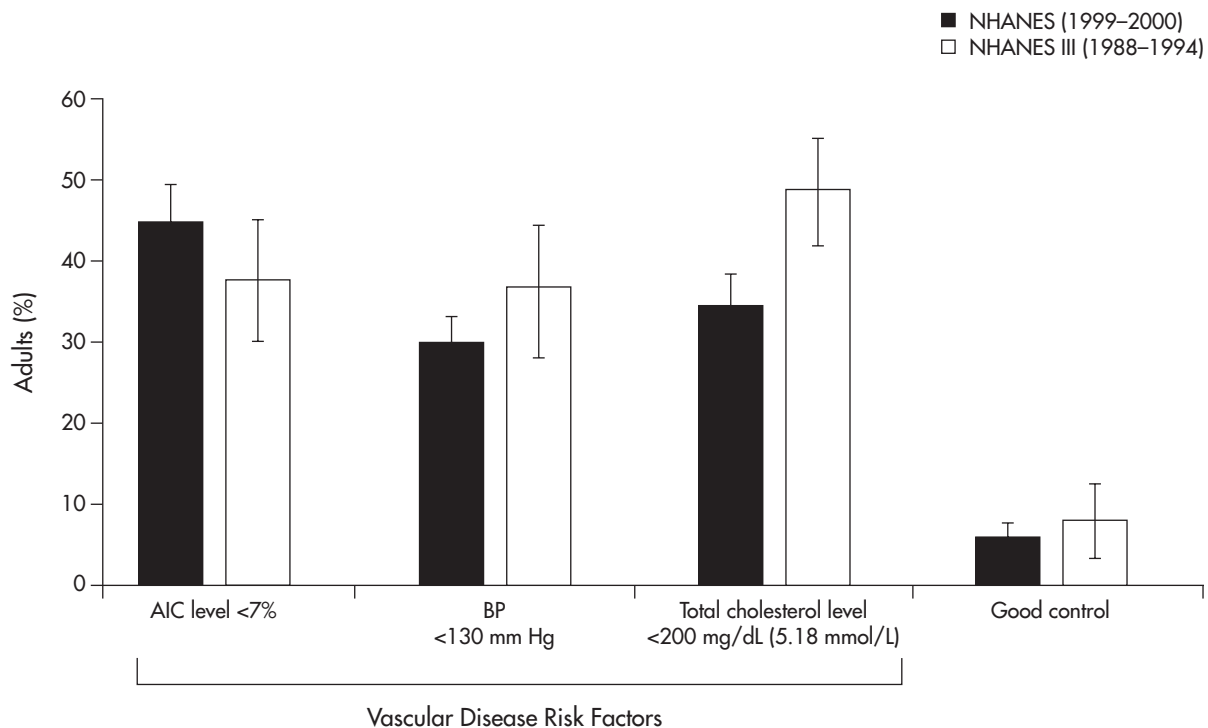


Figure 3. Percentages of adults with type 2 diabetes who were at the recommended levels for vascular risk factors in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) and NHANES 1999–2000. A1C = glycosylated hemoglobin; BP = blood pressure. Reproduced with permission from Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335–342. © Copyright 2004, American Medical Association. All rights reserved.

high (9.1%) in the DM cohort within 5 years of diagnosis and was more than twice the rate for the general population, supporting the need for aggressive early cardiovascular risk management in patients with type 2 DM.

HEART FAILURE AND DIABETES

Heart failure is the most common cause of hospitalization in older patients and commonly coexists with type 2 DM. In the Framingham study, the proportion of heart failure cases explained by DM alone was 12% in women and 6% in men.¹⁷ Diabetes is an important risk factor for the development of heart failure, independent of hypertension or coronary artery disease, and patients with type 2 DM experience a higher rate of adverse outcomes from heart failure.¹⁸ One factor that may contribute to these adverse outcomes is diabetic cardiomyopathy, which is characterized by myocyte hypertrophy and interstitial fibrosis.¹⁸ In addition to cardiac structural abnormalities (ie, left ventricular hypertrophy), functional abnormalities have been reported, such as cardiac conduction

defects.¹⁹ Changes in coagulation parameters resulting in hypercoagulability and hyperfibrinolysis have also been detected in patients with type 2 DM and may play a role in the pathogenesis of cardiovascular complications.²⁰

METABOLIC SYNDROME AND CARDIOVASCULAR EVENTS

Metabolic syndrome is a cluster of commonly occurring cardiovascular risk factors. It is not surprising, therefore, that a recent meta-analysis²¹ of 37 studies involving 172,573 individuals showed that metabolic syndrome was associated with almost double the risk of cardiovascular events and death (relative risk [RR], 1.78; 95% CI, 1.58–2.00) compared with individuals without metabolic syndrome. For specific outcomes, the RR ranged from 1.60 (95% CI, 1.28–2.01) for coronary heart disease (CHD) to 2.18 (95% CI, 1.63–2.93) for any cardiovascular event. Not all studies provided separate results for men and women, but in the 7 studies that did, the association between metabolic syndrome and cardiovascular

events or death was a third higher in women than in men (RR, 2.63 vs 1.98; $P = 0.09$).

HYPERGLYCEMIA INCREASES CARDIOVASCULAR RISK

The level of A1C provides an estimate of the average blood glucose levels over the previous 8 to 12 weeks and gives a more accurate picture of diabetes control for a particular patient than do simple plasma glucose levels. Tight glycemic control substantially reduces the risk of diabetes-related complications. The United Kingdom Prospective Diabetes Study was the first study that examined glycemic targets for patients with type 2 DM with respect to the risk of microvascular end points.²² Patients with an A1C level of 7.0% had a 25% reduction in this risk ($P = 0.0099$) compared with those who had an A1C level of 7.9%. A later study showed that each 1% reduction in mean A1C was associated with reductions of 21% in the risk of any diabetes-related end point, 21% for diabetes-related death, 14% for MI, and 37% for microvascular complications (all, $P < 0.0001$).²³ The American Diabetes Association (ADA)^{2,24} and the Canadian Diabetes Association²⁴ recommend a general A1C goal of $<7\%$ and to consider targeting a normal A1C ($<6\%$) if it can be achieved without unacceptable hypoglycemic events. The American Association of Clinical Endocrinologists (AACE)^{24,25} recommends an A1C goal of $\leq 6.5\%$, while the International Diabetes Federation²⁶ recommends an A1C goal of $<6.5\%$. However, this degree of glycemic control requires a compliant and motivated patient, an informed and motivated physician, an appropriate treatment regimen, vigilant monitoring, and a close partnership between the patient and a multidisciplinary team of health care professionals to ensure accurate monitoring and appropriate actions.²⁷

Targeting hyperglycemia alone, however, does not reduce the excess risk found in people with type 2 DM, so aggressive treatment is also needed for other risk factors.¹¹ The ADA guidelines for the management of type 2 DM note that it is difficult for many patients to achieve the recommended glycemic targets with the therapies that are currently available.² One problem with many diabetes medications is that they cause weight gain, which is itself associated with future CVD events. However, as exemplified by the study conducted by Woerle et al,²⁸ an A1C $<7\%$ is achievable with the majority of patients without weight gain or severe hypoglycemia.

In addition to various insulin preparations, drug classes approved for treatment of diabetes include sulfonylureas (eg, glyburide, glipizide, glimepiride), thiazolidinediones (TZDs, eg, pioglitazone, rosiglitazone), glinides (eg, repaglinide, nateglinide), biguanides (eg, metformin), α -glucosidase inhibitors (eg, acarbose, miglitol), dipeptidyl peptidase (DPP)-4 inhibitors (eg, sitagliptin), and glucagon-like peptide-1 (GLP-1) mimetics (eg, exenatide). In general, for patients with A1C levels $<8.5\%$, sulfonylureas, metformin, TZDs, repaglinide, sitagliptin, and exenatide are equally efficacious and somewhat superior to nateglinide and α -glucosidase inhibitors.^{29,30} The ADA^{2,31} and AACE³² have published their recommended treatment approaches. Both the ADA and AACE agree that metformin is the preferred first-line drug for the treatment of type 2 DM.

HYPERTENSION IS COMMON IN DIABETES

Hypertension, defined as BP $\geq 130/80$ mm Hg in diabetic patients versus $\geq 140/90$ mm Hg in nondiabetic patients, is an extremely common comorbid condition in type 2 DM. Estimates show that hypertension affects 60% to 71% of patients with diabetes, depending on obesity, ethnicity, and age.³³⁻³⁵ Patients with type 2 DM who develop hypertension have some unique characteristics, such as a tendency to develop proteinuria, salt sensitivity with changes in extracellular volume, disturbances in BP patterns, and a tendency toward systolic hypertension.³⁶ A retrospective, cross-sectional study conducted in 362 patients with type 2 DM who were treated at an ambulatory care center showed that 79% of the patients had concomitant diabetes and hypertension.³⁷ The hypertension was controlled (BP <135 mm Hg) in 65% of those patients with both medical conditions.

Hypertension is a risk factor for cardiovascular morbidity and mortality. Hypertension increases the risk of both microvascular and macrovascular complications of diabetes, including stroke, coronary artery disease, peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy. Consequently, patients with type 2 DM should have BP checked at each visit and treated to a target of $<130/80$ mm Hg. Untreated hypertension can result in enlargement of the heart and heart failure, aneurysm, renal failure, vision impairment, and atherosclerosis.¹ A study conducted in population cohorts in the Asia-Pacific region indicated that, among patients with type 2 DM, each 10 mm Hg higher than the usual systolic BP was

associated with a greater risk of 18% for CHD, 29% for ischemic stroke, and 56% for hemorrhagic stroke.³⁸ Hypertension is also a risk factor for the development of type 2 DM. A 28-year follow-up of a subgroup of men with treated hypertension reported that 20% of the patients developed new-onset DM.³⁹ These patients had a significantly and independently higher risk of stroke morbidity and total mortality than patients who did not develop DM.

Treatment of hypertension reduces the risk of morbidity and mortality. In 1 study, each 10-mm Hg decrease in BP was associated with risk reductions of 12% for any complication related to diabetes, 11% for MI, 13% for microvascular complications, and 15% for diabetes-related death.⁴⁰ The main classes of agents used to treat hypertension are diuretics, β -blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers.⁴¹ The most commonly prescribed antihypertensives are β -blockers and ACE inhibitors, which together account for 58% of antihypertensive drugs prescribed in the United States.⁴¹

It has been estimated that >65% of patients with DM and hypertension will require 2 or more different antihypertensive drugs to reach the target BP of <130/85 mm Hg (Figure 4).⁴²⁻⁵⁹ ACE inhibitors have been recommended as the first-line antihypertensive treatment in patients with type 2 DM and with proteinuria.⁴⁶ A considerable risk of acute stroke remains in patients receiving treatment for concomitant type 2 DM and hypertension.⁴⁷ This residual risk indicates that patients are not being treated optimally for all of their cardiometabolic risk factors.

DIABETIC DYSLIPIDEMIA

Both the NCEP ATP III and ADA guidelines identify low-density lipoprotein (LDL) cholesterol as the first priority of lipid lowering; the optimal level is set at <100 mg/dL (2.6 mmol/L).⁴⁸ High-dose therapy with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) or combination therapy will be required for most patients with type 2 DM to achieve the optimal LDL goal of <70 mg/dL. The combination of ezetimibe, bile-acid

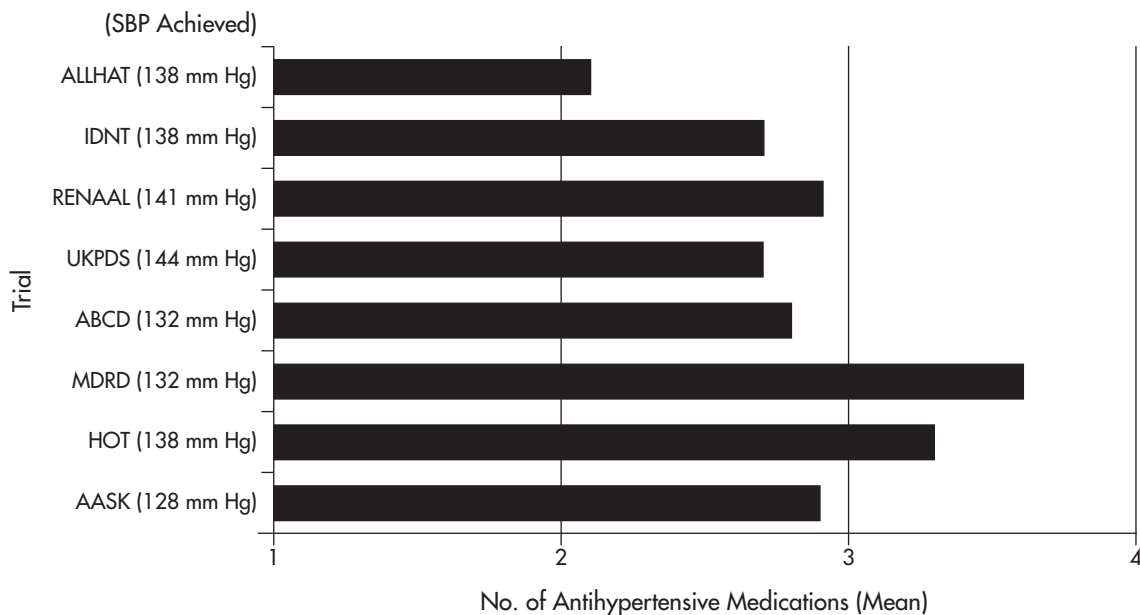


Figure 4. Mean number of antihypertensive agents needed per patient to achieve target systolic blood pressure (SBP) goals, by trial. Numbers in parentheses indicate the SBP goal in each study. ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; IDNT = Irbesartan Diabetic Nephropathy Trial; RENAAL = Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan; UKPDS = United Kingdom Prospective Diabetes Study; ABCD = Appropriate Blood Pressure in Diabetes; MDRD = Modification of Dietary Protein in Renal Disease; HOT = Hypertension Optimal Treatment; AASK = African-American Study of Kidney Disease. Reproduced with permission from Bakris GL. The importance of blood pressure control in the patient with diabetes. *Am J Med.* 2004;116(Suppl 1):30-38. © Copyright 2004, American Medical Association. All rights reserved.

TABLE II. THE MAIN LIPID ABNORMALITIES IN TYPE 2 DIABETES.

Lipoprotein	Plasma Level	Kinetic Abnormalities	Qualitative Abnormalities
VLDL	↑ (hypertriglyceridemia)	↑ Production ↓ Catabolism	Large VLDL (VLDL1) Glycation*
LDL	Normal or slightly ↑	↓ Catabolism ↓ Turnover	Small dense LDL (TG-rich LDL) Oxidation Glycation
HDL	↓	↑ Catabolism	TG-rich HDL Glycation

VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; HDL = high-density lipoprotein.

*Glycation is a nonenzymatic reaction between a sugar and the free amino groups of proteins.

Adapted with permission from Verges B. Diabetic dyslipidaemia: Insights for optimizing patient management. *Curr Med Res Opin.* 2005;21(Suppl 1):S29–S40.

sequestering agents, niacin, and fenofibrate with moderate doses of statins appears to be safe, but the long-term safety of combination therapy with high-dose statins remains to be demonstrated.⁴⁹

The dyslipidemia that occurs in type 2 DM consists of small dense LDL particles, elevations in remnant triglyceride (TG)-rich lipoprotein particles, and low levels of high-density lipoprotein (HDL) cholesterol (**Table II**).^{7,50} Treatment for diabetic dyslipidemia is generally directed toward lowering serum LDL-cholesterol levels with statins, leaving substantial excess risk of CVD in patients with these types of dyslipidemias. Evidence from landmark secondary-prevention studies has

shown that LDL lowering in type 2 DM is associated with significant clinical benefits (**Table III**).^{7,51–57} The correlation between cardiovascular event rates and LDL-cholesterol levels in trials comparing statin therapy with placebo is shown in **Figure 5**.⁵⁸

Trials investigating cardiovascular outcomes after treatment for dyslipidemia in patients with type 2 DM are listed in **Table IV**.^{57,59–69} The Collaborative Atorvastatin Diabetes Study (CARDS),⁶³ the first primary-prevention study of cholesterol lowering specifically in patients with type 2 DM, was conducted in 2838 patients in the United Kingdom and Ireland. Patients were randomized to placebo or atorvastatin 10 mg daily with an intended 6-year

TABLE III. LANDMARK TRIALS WITH SUBGROUP ANALYSES OF PATIENTS WITH DIABETES TREATED FOR DYSLIPIDEMIA.

Study	Intervention	No. of Patients with DM/ Total Population	Follow-up, y	Relative Risk Reduction
Statins				
HPS ⁵¹	Simvastatin	2912/20,536	5	↓33% in CV events
LIPID ⁵²	Pravastatin	782/9014	6.1	↓19% in CHD events
CARE ⁵³	Pravastatin	586/4159	5	↓25% in CHD events
4S ⁵⁴	Simvastatin	483/4398	5.4	↓42% in CHD risk
Fibrates				
VA-HIT ⁵⁵	Gemfibrozil	769/2531	5.1	↓32% in CHD risk
HHS ⁵⁶	Gemfibrozil	135/4081	5	↓68% in CHD risk

DM = diabetes mellitus; HPS = Heart Protection Study; CV = cardiovascular; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; CHD = coronary heart disease; CARE = Cholesterol and Recurrent Events; 4S = Scandinavian Simvastatin Survival Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; HHS = Helsinki Heart Study.

Adapted with permission from Hanefeld M. Outcome studies in type 2 diabetes. *Curr Med Res Opin.* 2005;21(Suppl 1):S41–S48.

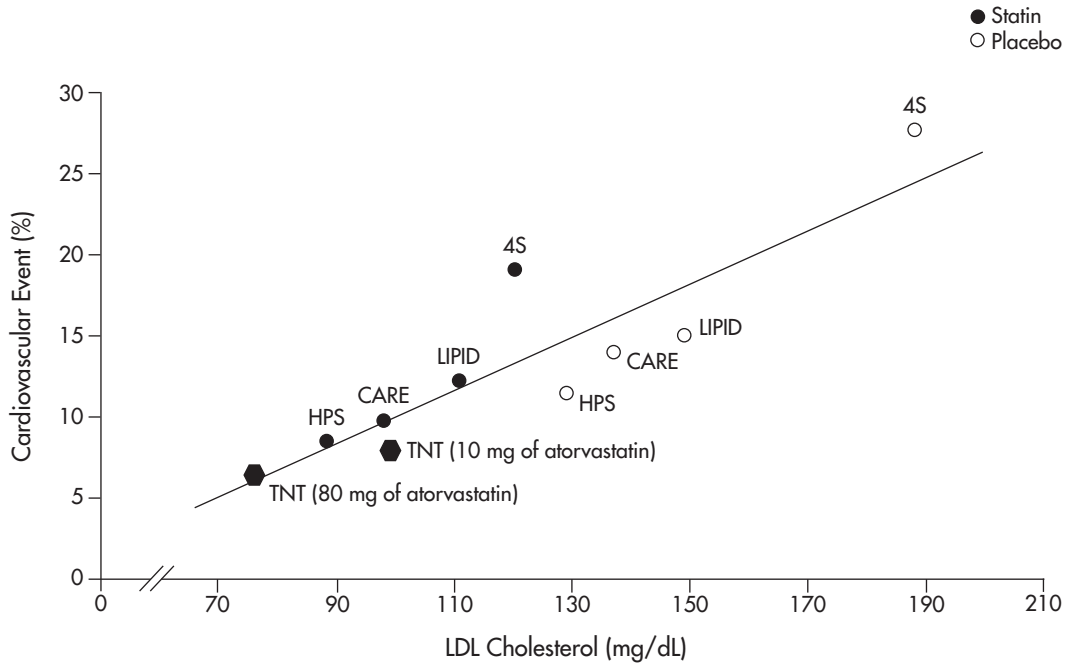


Figure 5. Correlation between cardiovascular event rates and low-density lipoprotein (LDL) cholesterol levels in trials comparing statin therapy with placebo. HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; 4S = Scandinavian Simvastatin Survival Study; TNT = Treating to New Targets. Reproduced with permission from LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425–1435. © Copyright 2005, Massachusetts Medical Society. All rights reserved.

follow-up. The primary end point was a composite of time to first occurrence of acute coronary event, coronary revascularization, or stroke. The primary composite end point favored the atorvastatin group ($P = 0.001$), and rates of individual end points were also significantly lower for patients randomized to atorvastatin. Forty percent reductions in LDL-cholesterol levels were observed, which are larger than usually seen in statin trials. The CARDS investigators concluded that all patients with type 2 DM should be considered for treatment with statins. However, one limitation of the study is that it was prematurely stopped after a median of 3.9 years when a significant difference in the primary end point was reached.

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus⁶⁶ was also conducted in a large patient population with type 2 DM and a history of CHD who were randomized to atorvastatin 10 mg daily or placebo. Two years into the study, the protocol was amended to

include patients without a history of CHD. The primary outcome was the time to the first occurrence of a composite end point of cardiovascular death, MI, stroke, recanalization, coronary artery bypass grafting, resuscitated cardiac arrest, or worsening angina requiring hospitalization. The results demonstrated no significant differences in primary or individual end points for all patients in either the primary- or secondary-prevention subgroup. However, the study was not powered to detect differences in primary- or secondary-prevention subgroups alone. Furthermore, a significant proportion (27%) of the placebo group was taking statin therapy. Thus, it is still an open question whether statin therapy should be initiated in all patients with type 2 DM in the absence of other cardiovascular risk factors.

Medication adherence can be an issue for patients with type 2 DM because of the multiple medications they are required to take to manage their various cardiometabolic risk factors. A study of 8408 patients enrolled in a

TABLE IV. DIABETES TRIALS INVESTIGATING CARDIOVASCULAR OUTCOMES AFTER TREATMENT FOR DYSLIPIDEMIA.

Study	Intervention	No. of Patients with DM/ Total Population	Follow-up	Relative Risk Reduction
UGDP ⁶⁰	Tolbutamide, insulin	823	5.5 y	Inconclusive
UKPDS ⁶¹	Metformin	342	10.7 y	↓39% in MI
DIS ⁶²	Clofibrate	1139	5 y	Inconclusive
DCCT ⁶³	Insulin	1441	6.5 y	↓41% in CV events
CARDS ⁶⁴	Atorvastatin	2838	3.9 y	↓37% in CV events
IDNT ⁶⁵	Irbesartan, amlodipine	1715	2.6 y	↓9% to 12% in CV events
RENAAL ⁶⁶	Losartan	1513	3.4 y	↓10% in CV risk
ASPEN ⁶⁷	Atorvastatin	2410	4 y	↓Nonsignificant in CV composite end point
PROactive ⁶⁸	Pioglitazone	5238	34.5 mo	↓Nonsignificant for risk of CV composite end point
PROactive 04 ⁶⁹	Pioglitazone	5238	34.5 mo	↓Significant for risk of recurrent stroke
FIELD ⁷⁰	Fenofibrate	9795	5 y	↓Nonsignificant (11%) for risk of MI or CHD death

DM = diabetes mellitus; UGDP = University Group Diabetes Program; UKPDS = United Kingdom Prospective Diabetes Study; MI = myocardial infarction; DIS = Diabetes Intervention Study; DCCT = Diabetes Control and Complications Trial; CV = cardiovascular; CARDS = Collaborative Atorvastatin Diabetes Study; IDNT = Irbesartan Diabetic Nephropathy Trial; RENAAL = Reduction of Endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; CHD = coronary heart disease.

Adapted with permission from Hanefeld M. Outcome studies in type 2 diabetes. *Curr Med Res Opin.* 2005;21(Suppl 1):S41–S48.

US managed-care health plan who initiated both hypertension treatment and lipid-lowering therapy found that the percentage of patients adherent with both therapies declined rapidly to 44.7%, 35.9%, and 35.8% at 3, 6, and 12 months, respectively.⁷⁰ Thus, most of the decrease in adherence occurred in the first 3 months.

ATHEROGENESIS IN DIABETES

Atherosclerosis is a complex process in which endothelial cell dysfunction plays a prominent role. Atherosclerotic lesions (atheromata) are asymmetric thickenings of the innermost layer of the artery, the intima. The atheroma is preceded by a fatty streak, an accumulation of lipid-containing cells beneath the endothelium. The cells present in the fatty streak are macrophages and some T cells. The endothelial cells produce cytokines, proteases, prothrombotic molecules, and vasoactive compounds. All of these secreted molecules can affect local inflammation and vascular function.⁷¹ Patients with type 2 DM experi-

ence a diffuse and accelerated progression of atherosclerosis. Atherosclerotic plaques are frequently more severe and at greater risk of subsequent complications.⁷² Diabetic plaques usually have a greater lipid core burden and a larger inflammatory component and are more commonly complicated by overlying thrombosis.⁷³ Insulin resistance can increase levels of very-low-density lipoprotein cholesterol, which contain high concentrations of TGs, resulting in high serum TG levels and low serum HDL-cholesterol levels.⁷⁴ Small dense LDL particles are highly atherogenic, more likely to form oxidized LDL, and less readily cleared. Low HDL-cholesterol is an independent risk factor for CVD.

INCREASED RISK OF MORBIDITY AND MORTALITY DUE TO SMOKING

Both abdominal adiposity and smoking contribute to insulin resistance and other metabolic derangements.⁷⁵ In the INTERHEART study,⁹ smoking was as important a

risk factor for MI as dyslipidemia, hypertension, and diabetes. A heightened risk of morbidity and premature death is associated with the development of macrovascular complications among diabetic patients who smoke.^{2,76,77} Smoking is also related to the premature development of microvascular complications of diabetes.² Cigarette smoking is a modifiable risk factor for increased mortality in women with type 2 DM⁷⁷ and for the development of type 2 DM in men.⁷⁸

ADA guidelines recommend that health care providers advise all smokers with type 2 DM to quit smoking because of the adverse health effects.^{2,79} Smoking cessation has been associated with improvement in A1C levels⁸⁰ and can have a positive impact on cardiovascular health, particularly in patients with type 2 DM. Although smoking cessation is associated with weight gain, the overall cardiovascular benefit of quitting is greater than the risk due to weight gain.⁷⁸

NEW PARADIGMS IN RISK REDUCTION THERAPIES

The current approach involves treatment of individual risk factors but underemphasizes that these factors are continuous rather than categorical and that they have additive effects. Because cardiometabolic risk factors tend to cluster and are continuous rather than categorical, patients generally have been treated late in the natural history of the disease. These subclinical conditions could be discovered through a comprehensive evaluation of the patient, which would allow recommendations for optimal treatment to address all of the risk factors.¹

KEY POINT

The current approach involves treatment of individual risk factors but underemphasizes that these factors are continuous rather than categorical and that they have additive effects.

Therapeutic lifestyle changes are considered primary therapies for hyperglycemia in type 2 DM because they are considered to be inexpensive, natural, and without the side effects that accompany drug therapy. There are numerous studies demonstrating the effectiveness of lifestyle interven-

tions (eg, diet and exercise) with and without pharmacotherapy.^{81,82} The problem, however, is that patients often find it difficult to sustain these lifestyle changes and therefore to maintain the resulting weight loss and cardiovascular benefit.⁸³ One option for some morbidly obese and super-obese individuals may be surgery.⁸⁴ New pharmacotherapeutic agents may also be appropriate options.

Because no treatment is 100% effective in all patients, there is residual risk with any given therapy. This residual risk is particularly evident in patients with multiple risk factors.¹ Patients may also have gaps in treatment because medications are usually indicated for 1 or maybe 2 risk factors. Thus, the optimal treatment of multiple risk factors requires multiple prescriptions. Currently, the focus in treatment is on preventing CVD rather than controlling glucose, lipid, or BP levels. A number of medications with novel mechanisms of action have been evaluated recently for the treatment of patients with type 2 DM and multiple cardiometabolic risk factors.

Fibrates: PPAR- α Agonists

Fibrates (fenofibrate, bezafibrate, gemfibrozil) activate the nuclear transcription factor peroxisome proliferator-activated receptor- α (PPAR- α). Activation of PPAR- α results in increased lipolysis and clearance of atherogenic TG-rich lipoproteins.⁸⁵ Fibrates also have pleiotropic effects that are not related to lipids, such as reductions in fibrinogen, C-reactive protein, proinflammatory cytokines (interleukin-6, tumor necrosis factor- α), and uric acid levels; improvements in flow-mediated dilatation; and increases in homocysteine levels.⁸⁵ Fibrates decrease TGs more than statins do and increase HDL-cholesterol levels, especially when baseline levels are low.^{50,86}

Favorable results have been reported in some fibrate trials that contained subgroups of patients with type 2 DM, such as the Veterans Affairs High-Density Lipoprotein Intervention Trial⁵⁵ and the Helsinki Heart Study.⁵⁶ The Fenofibrate Intervention and Event Lowering in Diabetes study⁷¹ examined the efficacy of fenofibrate in reducing cardiovascular morbidity in type 2 DM. After 5 years, there was a nonsignificant 11% reduction in the primary end point (the risk of MI or CHD death) for fenofibrate compared with placebo.

Thiazolidinediones: PPAR- γ Agonists

The nuclear transcription factor PPAR- γ is expressed most abundantly in adipose tissue, but it is also found in pan-

creatic β -cells, vascular endothelium, and macrophages.⁸⁷ Its expression is low in the liver, heart, and skeletal muscle—tissues that express predominantly PPAR- α . PPAR- γ agonists have several antiatherogenic properties, such as increasing TG lipolysis, free fatty acid transport, and conversion of free fatty acids to TGs. TZDs have variable effects on HDL-cholesterol and TG levels, as well as beneficial nonlipid effects, such as regulating mediators involved in inflammation, endothelial dysfunction, monocyte and macrophage function, and fibrinolysis.

TZDs promote fatty acid uptake and storage in adipose tissue, thus increasing adipose tissue mass and sparing insulin-sensitive tissues such as skeletal muscle and liver from the harmful effects of high concentrations of free fatty acids. Troglitazone was the first TZD approved in the United States in 1997, but the drug was removed from the market because of safety concerns (hepatotoxicity). The TZDs currently available in the United States are rosiglitazone and pioglitazone, both approved in 1999.^{88,89}

Dipeptidyl Peptidase-4 Inhibitors

The gastrointestinal incretin hormones (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]) are released when food is ingested; they enhance the glucose-dependent insulin response and suppress the glucagon response.⁹⁰ However, GLP-1 and GIP undergo rapid enzymatic degradation by DPP-4. DPP-4 inhibitors are a new class of antihyperglycemic drugs that slow the inactivation of GLP-1 and GIP. These agents are not likely to produce hypoglycemia as an adverse effect, may have beneficial effects on β -cell function, and can be administered orally.

Sitagliptin was approved by the US Food and Drug Administration in October 2006 and has shown significantly better efficacy than placebo in reducing A1C when used as add-on therapy in patients with suboptimal glycemic control with oral antihyperglycemic drugs.^{91,92} Sitagliptin was also shown to be effective as monotherapy in patients with type 2 DM.^{93,94}

Incretin Mimetics

Exenatide is the first drug in a new drug class called incretin mimetics. Exenatide is a synthetic peptide with incretin properties similar to those of GLP-1. It is resistant to enzymatic degradation by DPP-4 and has a glucoregulatory potency that is up to 3000-fold greater than that of native GLP-1.⁹⁵ Therapeutic actions of exenatide

include decreasing inappropriate glucagon secretion, decreasing overall food intake by delaying gastric emptying, and preventing hyperglycemic episodes by targeting postprandial insulin responses. Exenatide is intended for use as adjunctive therapy in patients with type 2 DM who have not achieved adequate glycemic control with metformin, a sulfonylurea, or the combination of both medications. The drug is injected twice daily before morning and evening meals.

CONCLUSIONS

CVD is the major cause of mortality for individuals with type 2 DM, in part because type 2 DM often coexists with other cardiometabolic risk factors such as hypertension and dyslipidemia. In fact, targeting hyperglycemia alone does not reduce the excess risk in type 2 DM, so aggressive treatment is also needed for the other risk factors. Currently, the focus is on preventing CVD rather than just controlling glucose, lipid, or BP levels. Several medication classes are available for the different cardiometabolic risk factors, including antihyperglycemic, antihypertensive, and lipid-lowering agents. The primary treatment is lifestyle change, followed by LDL-cholesterol lowering with statins. Combinations of drugs with different mechanisms of action are frequently used, but patients with type 2 DM still have a residual risk of cardiovascular events. Thus, new drugs are still needed and are in development to reduce the morbidity and mortality from cardiovascular events in patients with diabetes.

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REFERENCES

1. Watson K. Managing cardiometabolic risk: An evolving approach to patient care. *Crit Pathw Cardiol.* 2007;6:5–14.
2. ADA. Standards of medical care in diabetes—2007. *Diabetes Care.* 2007;30(Suppl 1):S4–S41.
3. Haffner SM, Lehto S, Ronnema 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;339:229–234.
4. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. *Circulation.* 2007;115:1544–1550.
5. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American Heart

- Association and the American Diabetes Association. *Diabetes Care*. 2007;30:162–172.
6. Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med*. 2002;347:1342–1349.
 7. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. *Diabetes Care*. 1999;22:233–240.
 8. Carmena R, Betteridge DJ. Statins and diabetes. *Semin Vasc Med*. 2004;4:321–332.
 9. Yusuf S, Hawken S, Ounpuu S, et al, for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*. 2004;364:937–952.
 10. Coccheri S. Approaches to prevention of cardiovascular complications and events in diabetes mellitus. *Drugs*. 2007;67:997–1026.
 11. Erdmann E. Diabetes and cardiovascular risk markers. *Curr Med Res Opin*. 2005;21(Suppl 1):S21–S28.
 12. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: A call to action from the American Diabetes Association and the American Heart Association. *Diabetes Care*. 2006;29:1697–1699.
 13. Schneider CA. Improving macrovascular outcomes in type 2 diabetes: Outcome studies in cardiovascular risk and metabolic control. *Curr Med Res Opin*. 2006;22(Suppl 2):S15–S26.
 14. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335–342.
 15. Massi-Benedetti M. Changing targets in the treatment of type 2 diabetes. *Curr Med Res Opin*. 2006;22(Suppl 2):S5–S13.
 16. Jeerakathil T, Johnson JA, Simpson SH, Majumdar SR. Short-term risk for stroke is doubled in persons with newly treated type 2 diabetes compared with persons without diabetes: A population-based cohort study. *Stroke*. 2007;38:1739–1743.
 17. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557–1562.
 18. Masoudi FA, Inzucchi SE. Diabetes mellitus and heart failure: Epidemiology, mechanisms, and pharmacotherapy. *Am J Cardiol*. 2007;99:113B–132B.
 19. Movahed MR. Diabetes as a risk factor for cardiac conduction defects: A review. *Diabetes Obes Metab*. 2007;9:276–281.
 20. Bolaman Z, Kok F, Kadikoylu G, et al. The changes of coagulation parameters and microvascular complications in diabetes mellitus. *Endocrinologist*. 2007;17:196–199.
 21. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–414.
 22. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
 23. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*. 2000;321:405–412.
 24. Qaseem A, Vijan S, Snow V, et al, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Glycemic control and type 2 diabetes mellitus: The optimal hemoglobin A_{1c} targets. A guidance statement from the American College of Physicians. *Ann Intern Med*. 2007;147:417–422.
 25. Unger J. Practical strategies for achieving targeted glycaemic control in patients with type 2 diabetes. *J Fam Pract*. 2006;55:S25–S32.
 26. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Chapter 6: Glucose control levels. <http://www.idf.org/webdata/docs/GGT2D%2006%20Glucose%20control%20levels.pdf>. Accessed October 16, 2007.
 27. LeRoith D, Smith DO. Monitoring glycaemic control: The cornerstone of diabetes care. *Clin Ther*. 2005;27:1489–1499.
 28. Woerle HJ, Tenner S, Irsigler A, et al. Impact of fasting and postprandial glycemia on overall glycaemic control in type 2 diabetes. Importance of postprandial glycemia to achieve target HbA_{1c} levels. *Diabetes Res Clin Pract*. 2007;77:280–285.
 29. Bolen S, Feldman L, Vassy J, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;147:386–399.
 30. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. Scientific review. *JAMA*. 2002;287:360–372.
 31. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29:1963–1972.
 32. ACE/AACE Diabetes Road Map Task Force. Road maps to achieve glycaemic control in type 2 diabetes mellitus. *Endocrine Pract*. 2007;13:260–268.
 33. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. *Diabetes Care*. 2002;25:134–147.
 34. Geiss LS, Rolka DB, Engelgau MM. Elevated blood pressure among U.S. adults with diabetes, 1988–1994. *Am J Prev Med*. 2002;22:42–48.
 35. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med*. 2003;138:593–602.
 36. Tan AS, Kuppuswamy S, Whaley-Connell AT, et al. Recommendations for special populations—the treatment of hypertension in diabetes mellitus. *Endocrinologist*. 2004;14:368–381.
 37. Choe HM, Townsend KA, Blount G, et al. Treatment and control of blood pressure in patients with diabetes mellitus. *Am J Health Syst Pharm*. 2007;64:97–103.
 38. Kengne AP, Patel A, Barzi F, et al. Systolic blood pressure, diabetes and the risk of cardiovascular diseases in the Asia-Pacific region. *J Hypertens*. 2007;25:1205–1213.

39. Almgren T, Wilhelmsen L, Samuelsson O, et al. Diabetes in treated hypertension is common and carries a high cardiovascular risk: Results from a 28-year follow-up. *J Hypertens*. 2007;25:1311–1317.
40. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *BMJ*. 2000;321:412–419.
41. Smith ET, Ashiya M. Antihypertensive therapies. *Nat Rev Drug Discov*. 2007;6:597–598.
42. Sowers JR, Reed J. 1999 Clinical Advisory Treatment of Hypertension and Diabetes. *J Clin Hypertens (Greenwich)*. 2000;2:132–133.
43. Dobesh PP. Managing hypertension in patients with type 2 diabetes mellitus. *Am J Health Syst Pharm*. 2006;63:1140–1149.
44. Bakris GL, Williams M, Dworkin L, et al, for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Special report. Preserving renal function in adults with hypertension and diabetes: A consensus approach. *Am J Kid Dis*. 2000;36:646–661.
45. Bakris GL. The importance of blood pressure control in the patient with diabetes. *Am J Med*. 2004;116(Suppl 1): 30–38.
46. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: An update. *Hypertension*. 2001;37:1053–1059.
47. Junga K, Merlo J, Gullberg B, et al. Residual risk for acute stroke in patients with type 2 diabetes and hypertension in primary care: Skaraborg Hypertension and Diabetes Project. *Diabetes Obes Metab*. 2006;8:492–500.
48. Haffner SM. Dyslipidemia management in adults with diabetes. *Diabetes Care*. 2004;27(Suppl 1):S68–S71.
49. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol*. 2007;49:1753–1762.
50. Verges B. Diabetic dyslipidaemia: Insights for optimizing patient management. *Curr Med Res Opin*. 2005;21(Suppl 1): S29–S40.
51. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
52. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
53. 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;98:2513–2519.
54. Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: Subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999; 159:2661–2667.
55. 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;162:2597–2604.
56. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care*. 1992;15:820–825.
57. Hanefeld M. Outcome studies in type 2 diabetes. *Curr Med Res Opin*. 2005;21(Suppl 1):S41–S48.
58. LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
59. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes*. 1970;19(Suppl):789–830.
60. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.
61. Hanefeld M, Fischer S, Schmechel H, et al. Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care*. 1991;14:308–317.
62. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986.
63. 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;364:685–696.
64. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
65. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001; 345:861–869.
66. Knopp RH, d’Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–1485.
67. 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;366:1279–1289.
68. Wilcox R, Bousser MG, Betteridge DJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: Results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke*. 2007;38:865–873.

69. 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;366:1849–1861.
70. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med*. 2005;165:1147–1152.
71. Sigal LH. Basic science for the clinician 44: Atherosclerosis: An immunologically mediated (autoimmune?) disease. *J Clin Rheumatol*. 2007;13:160–168.
72. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. *J Am Coll Cardiol*. 2003;41:1071–1077.
73. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation*. 2000;102:2180–2184.
74. Nesto RW. Beyond low-density lipoprotein: Addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs*. 2005;5:379–387.
75. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875–880.
76. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. *Diabetes Care*. 1999;22:1887–1898.
77. Al-Delaimy WK, Willett WC, Manson JE, et al. Smoking and mortality among women with type 2 diabetes: The Nurses' Health Study cohort. *Diabetes Care*. 2001;24:2043–2048.
78. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care*. 2001;24:1590–1595.
79. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. *Diabetes Care*. 2003;26(Suppl 1):S89–S90.
80. Gunton JE, Davies L, Wilmshurst E, et al. Cigarette smoking affects glycemic control in diabetes. *Diabetes Care*. 2002;25:796–797.
81. Kelley DE, Kuller LH, McKolanis TM, et al. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. *Diabetes Care*. 2004;27:33–40.
82. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
83. Dansinger ML, Tatsioni A, Wong JB, et al. Meta-analysis: The effect of dietary counseling for weight loss. *Ann Intern Med*. 2007;147:41–50.
84. Wolf AM, Beisiegel U. The effect of loss of excess weight on the metabolic risk factors after bariatric surgery in morbidly and super-obese patients. *Obes Surg*. 2007;17:910–919.
85. Keating GM, Croom KF. Fenofibrate: A review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs*. 2007;67:121–153.
86. Verges B. Fenofibrate therapy and cardiovascular protection in diabetes: Recommendations after FIELD. *Curr Opin Lipidol*. 2006;17:653–658.
87. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351:1106–1118.
88. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457–2471.
89. Dormandy JA, Charbonnel B, Eckland DJ, et al, for the PROactive Investigators. 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;366:1279–1289.
90. Lyseng-Williamson KA. Sitagliptin. *Drugs*. 2007;67:587–597.
91. Rosenstock J, Brazg R, Andryuk PJ, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2006;28:1556–1568.
92. Brazg R, Xu L, Dalla Man C, et al. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:186–193.
93. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006;29:2632–2637.
94. Raz I, Hanefeld M, Xu L, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia*. 2006;49:2564–2571.
95. Cvetkovic RS, Plosker GL. Exenatide: A review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea). *Drugs*. 2007;67:935–954.

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Dialogue Box

EDITORIAL BOARD

What is the pathogenesis of diabetic cardiomyopathy?

GERICH

It is unclear whether it represents a microvascular or macrovascular complication. We tend to lean toward a microvascular one because it seems to involve small vessels in a somewhat patchy distribution, as opposed to disease in a large coronary vessel. As a result, it is not accessible to an angioplasty or a surgical intervention.

EDITORIAL BOARD

Is it a cause for patients who have heart attacks despite normal coronary angiograms?

GERICH

Yes. And these people also are more prone to developing heart failure.

EDITORIAL BOARD

When shooting for a target blood pressure of <130/80 mm Hg in patients with diabetes, clinicians will sometimes experience difficulty getting the systolic pressure down to goal without bottoming out the diastolic. How would you manage such a patient?

GERICH

Although that can be a problem, it is equally a problem in people without diabetes. Suffice it to say that I'd back off on lowering the systolic pressure further if the diastolic begins to dip below 60 mm Hg, especially in elderly people, and accept the higher systolic pressure.

EDITORIAL BOARD

What low-density lipoprotein cholesterol (LDL-C) level do you target in patients with diabetes?

GERICH

Although the National Cholesterol Education Program generally recommends a target LDL-C of <100 mg/dL for patients with diabetes and <70 mg/dL primarily for patients with diabetes and known coronary heart dis-

ease, I generally shoot for the latter in all of my diabetic patients >40 years of age. I keep asking my cardiology colleagues if you can have an LDL-C that is too low and they always say "no."

EDITORIAL BOARD

What are your thoughts about the Nissen meta-analysis regarding thiazolidinediones (TZDs) in patients with diabetes?

GERICH

Dr. Nissen's analysis is controversial because it depends on what statistics you use. Furthermore, the PROspective pioglitAzone Clinical Trial in macroVascular Events (PROACTIVE) study was negative because it didn't correct for multiple comparisons. Suffice it to say that there is no evidence that TZDs, independent of improving glycemic control, have a beneficial effect on cardiovascular disease. Thus, a lot of the reason for using them in the first place has vanished. You know they were promoted as providing an added benefit on top of improving glycemia. That has not proved to be the case. Even before the Nissen study, I usually relegated them to a second- or third-tier therapy because they were more expensive than metformin, took a longer time to get to a maximum effect, and had more side effects. As expressed by others, I can't think of a positive reason why someone would choose to start a patient on a TZD as opposed to one of the other drugs currently available.

EDITORIAL BOARD

Would you use them to achieve better glycemic control in a patient already on metformin and a sulfonylurea?

GERICH

In such a patient, I generally wouldn't add a third pill. I would likely add basal insulin therapy which would be more cost-effective. I primarily use TZDs in patients unable to tolerate metformin or who have a contraindication.

Dialogue Box

EDITORIAL BOARD

Are fibrates and niacins underutilized in patients with type 2 diabetes?

GERICH

I think niacin is. I don't think fibrates are. Niacin is underused because of the fear that it may induce insulin resistance and make the diabetes worse—in reality, its effect on glycemic control is rather small and can be overcome by dose adjustment of the diabetic medications.

EDITORIAL BOARD

When do you use niacin?

GERICH

I generally use niacin in patients with hypertriglyceridemia, particularly in patients in whom fibrates can't be used. I generally use fibrates as first-line therapy because there are more data with them and you don't have issues with flushing or the potential for deterioration in glycemic control.

EDITORIAL BOARD

Aren't you reluctant to add a fibrate to a patient already taking a statin because of the risk of rhabdomyolysis?

GERICH

You know, I have never seen this myopathy and I often use a fibrate and a statin together. I warn patients about muscle pains, but I have been at the University of Rochester now 14 years and neither I nor my colleagues have ever had a case. This is pretty uncommon—it is almost like an idiosyncratic reaction.

EDITORIAL BOARD

How important is the glycemic index of carbohydrates?

GERICH

I am really not much of a believer in the glycemic index because it wasn't generated with meals and whether you eat potatoes or rice as part of a meal makes a big difference. For years, we told people not to drink Coca Cola. Although we still don't recommend it because of calories, it makes a big difference whether you drink it with a meal or not.