Treating the Diabetic Patient: Appropriate Care for Glycemic Control and Cardiovascular Disease Risk Factors

Stuart W. Zarich, MD, FACC

Yale University School of Medicine, New Haven, CT, and Department of Cardiovascular Medicine, Bridgeport Hospital, Bridgeport, CT

Diabetes, a leading cause of morbidity and mortality in the United States, is associated with a 2- to 4-fold increase in the risk of coronary artery disease. As the population in the United States has aged, the incidence of obesity, hypertension, glucose intolerance, and dyslipidemia has increased significantly, culminating in the current epidemic of type 2 diabetes mellitus. Strict glycemic control must, therefore, be accompanied with proven therapies (such as antihypertensives and lipid-lowering agents) to reduce cardiovascular events. Patients with type 2 diabetes have average low-density lipoprotein (LDL) levels but have an increased number of small, dense LDL particles, which are associated with a 3-fold increase in cardiovascular disease. Type 2 diabetes mellitus is also associated with increased triglyceride rich atherogenic particles, which trigger inflammation. In addition to glycemic control and drug therapy, lifestyle modifications (eg, diet, weight loss, and exercise) also play an important role in managing diabetes. Therefore, strict glycemic control, pharmacologic therapy, and lifestyle modifications are parts of a comprehensive strategy to prevent both microvascular and macrovascular events in patients with type 2 diabetes.
[Rev Cardiovasc Med. *2003;4(suppl 6):S19-S28*]

Key words: Glycemic control • Dyslipidemia • Glucose intolerance • Hypertension • Cardiovascular disease

Diabetes is the leading cause of morbidity and mortality in the United States. Diabetes is associated with a 2- to 4-fold increase in the risk of coronary artery disease.[1] As the population in the United States has aged, the incidence of the deadly quartet (obesity, hypertension, glucose intolerance, and dyslipidemia) has markedly increased,[2] culminating in the current epidemic

Table 1
Pathophysiologic Mechanisms Contributing to Macrovascular Disease in Type 2 Diabetes Mellitus

- Atherogenic dyslipidemia
  - Small, dense low-density lipoprotein
  - Hypertriglyceridemia
  - Low high-density lipoprotein levels
- Hypercoagulable state
  - Increased plasminogen activator inhibitor-1 levels
  - Increased fibrinogen levels
  - Platelet hyperreactivity
- Proinflammatory state
  - Increased hsCRP levels
  - Increased tumor necrosis factor-α production by adipocytes
  - Increased oxidized low-density lipoprotein
- Advanced glycosylated end products
- Endothelial dysfunction
- Lipotoxicity
- Glucotoxicity
- Hyperinsulinemia
- Hypertension
- Leptin resistance

hsCRP, high-sensitivity C-reactive protein.

of type 2 diabetes mellitus. Of all individuals who have diabetes, approximately 85% to 90% have type 2; it typically affects older patients, especially those over the age of 50. Diabetes mellitus is now considered a "cardiovascular [CV] risk equivalent" because patients with type 2 diabetes and no prior history of CV disease have the same future risk of having a myocardial infarction (MI) as nondiabetics with a prior history of MI.[3]

Glycemic Control and Cardiovascular Events

Multiple mechanisms contribute to the increased risk of CV disease in type 2 diabetes (Table 1), but an exhaustive review is beyond the scope of this paper. Traditional CV risk factors associated with type 2 diabetes account for only 25% to 50% of the increased CV risk associated with diabetes.[4] Insulin resistance at the musculoskeletal levels results in hyperglycemia, increased level of circulating free fatty acids, and compensatory hyperinsulinemia. Insulin resistance in itself is associated with a 2-fold increase in CV events, even when corrected for traditional CV risk factors.[5] Hepatic production of triglyceride rich lipoproteins results in a reciprocal decrease in high-density lipoprotein (HDL). Adipocytes release proinflammatory cytokines (interleukin-6 and tumor necrosis factor-α), which can directly promote atherogenesis and also elicit the hepatic production of C-reactive protein and fibrinogen, and increase plasminogen activator inhibitor-1 levels. Recent evidence also implicates the role of CD40 signaling in chronic inflammation and atherogenesis in diabetic subjects.[6] Advanced glycosylated end products (AGE) further increase inflammatory mediators and oxidative stress and appear to similarly play a major role in atherogenesis.

Given that glycemic control reduces nonenzymatic glycation of hemoglobin, as reflected in glycosylated hemoglobin (HbA_{1c}) levels, one would postulate that strict glycemic control would reduce CV complications in type 2 diabetes. Although clinical trials have definitively shown a direct correlation between strict glycemic control and a reduction in microvascular complications (eg, nephropathy, retinopathy, and neuropathy), the relationship between tight glycemic control and reduction of macrovascular events has been less clear.[7] Although strict glycemic control lowers the risk of microvascular events to a greater extent than macrovascular events, pharmacologic interventions targeting hypertension and dyslipidemia have markedly reduced CV events in patients with type 2 diabetes.

Potential complicating factors in the relationship between glycemic control and macrovascular events are shown in Table 2. The United Kingdom Prospective Diabetes Study (UKPDS) found only a borderline association between glucose control and the risk of MI (16%

Insulin resistance in itself is associated with a 2-fold increase in cardiovascular (CV) events, even when corrected for traditional CV risk factors.

Table 2
Potential Explanations for the Lack of Clear Association Between Glycemic Control and Macrovascular Events

- Clinical studies were underpowered for macrovascular events
- Strict, durable glycemic control not obtained
- Little experience with insulin sensitizers
- Sulfonylureas may have adverse cardiovascular effects
- Duration of studies limited (especially in light of lack of durable glycemic control) and therapy started late in the course of type 2 diabetes
- Contribution of other macrovascular risk factors

reduction, $P = .052$).[8] Each 1% reduction in HbA_{1c} levels resulted in a 14% decrease in MI compared with a 37% decrease in microvascular events. However, this study may have been underpowered due to a paucity of macrovascular events (4.1% incidence of MI over 6 years) in this population of patients with new-onset type 2 diabetes mellitus. In addition, both the degree and durability of glycemic control have been questioned as HbA_{1c} levels rose progressively in both the intensively and conservatively treated groups and the treatment goal of a fasting glucose below 6 mmol/L was not attained. At 6 years, the median HbA_{1C} levels had risen from 6.1% to 7.1% in the intensive group because of the progressive deterioration in ß cell function. For the 10-year duration of the study, only an 11% difference was maintained between the intensively and conservatively treated groups.

The cardiovascular profiles of the various hypoglycemic interventions used may have also played a role in the relative lack of success in reducing macrovascular events. In the University Group Diabetes Program (UGDP) study, tolbutamide was associated with an increased CV risk in patients with type 2 diabetes.[9] Sulfonylureas may worsen CV outcomes due to a detrimental effect on ischemic preconditioning through its action on adenosine triphosphate (ATP)–dependent potassium channels and increased insulin secretion.[10] Insulin, sulfonylurea, and short-acting insulin secretagogues have little to no effect on improving insulin sensitivity and thus, unlike the insulin sensitizers (metformin and thiazolidinediones), have little effect on the proinflammatory, prothrombotic, and oxidative consequences of insulin resistance. Although the UKPDS did not suggest a detrimental CV effect of sulfonylureas, a recent observational study involving patients with type 2 diabetes undergoing primary angioplasty showed that sulfonylureas were associated with a 2.8-fold increased risk of early mortality.[11]

Sulfonylureas may worsen CV outcomes due to a detrimental effect on ischemic preconditioning through its action on adenosine triphosphate–dependent potassium channels and increased insulin secretion.

In contrast to the results with insulin and sulfonylureas, MI was reduced 39% ($P = .01$) in the metformin arm of UKPDS despite similar glycemic control in obese patients with type 2 diabetes (although the benefit was not seen with metformin in combination with insulin or sulfonylureas).[12] Observational studies have also suggested a CV benefit of insulin sensitizers versus insulin providers. In the Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) I and II trials,[13] metformin or thiazolidinedione was associated with fewer CV events than insulin or sulfonylurea therapy in over 3000 diabetics with acute coronary syndromes. In a recent case-control study of first MI in patients with type 2 diabetes, thiazolidinedione was associated with an odds ratio for MI of 0.40 (95% CI, 0.2-0.8), while there was no association between insulin, metformin, or sulfonylureas and MI occurrence.[14]

Thiazolidinediones may hold particular promise with their direct effects on the arterial wall and smooth muscle cells[15] as well as a host of salutary nonhypoglycemic effects[16] on proinflammatory and prothrombotic CV risk factors (Table 3). In experimental MI models, rosiglitazone therapy reduces infarct size and improves left ventricular remodeling.[17,18] In placebo-controlled trials, thiazolidinediones lower HbA_{1c} levels to a similar extent as metformin and sulfonylureas and more than the α-glucosidases.[19]

Previous studies of glycemic control may have started too late in the time course of type 2 diabetes mellitus. Because diabetes is typically diagnosed relatively late in its course, vascular disease is frequently present at the time of diagnosis. As summarized in Table 4, current studies are underway to address earlier treatment of insulin resistant

Table 3
Effects of Thiazolidinediones on Cardiovascular Risk Factors

Risk Factors	Effect
Atherogenic dyslipidemia	↓ Sd LDL
	↑ HDL
	↓ (or no effect) Triglycerides
Hypercoagulable state	↓ PAI-1
	↓ Fibrinogen
	↓ Platelet aggregation
Central obesity	↓ Visceral fat
	↑ Adiponectin levels
	↓ CRP, MMP-9
Inflammation	↓ Effects TNFα
	↓ Soluble CD40
	↓ VCAM/ICAM expression
	Inhibit NF-κB
	Inhibit RAGE expression
Direct vascular effects	Improve endothelial function
	Lower blood pressure
	Reverse carotid IMT
	Prevent in-stent restenosis

Sd, small dense; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein; MMP, matrix metalloproteinase; TNFα, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; RAGE, receptor for advanced glycosylated end products; IMT, intimal-medial thickness;NF-κB, nuclear factor kappa B.

patients (prior to the development of overt type 2 diabetes) and to examine the role of insulin providers versus insulin sensitizers in reducing macrovascular events in patients with established type 2 diabetes mellitus. Prior studies of glycemic control may have also suffered from too short a duration of therapy given the lack of durable control achieved.[20] The following article by Dr Edelman discusses recent studies with the thiazolidinediones showing more durable control compared with conventional agents. These outcomes have been attributed to pancreatic ß cell preservation.[21] Strict glycemic control should be attained to reduce microvascular events, with the hope that macrovascular event reduction will be more evident in future trials if improvements in insulin sensitivity and more durable glycemic control can be attained.

Strict glycemic control should also be the goal in the setting of acute MI in diabetic subjects. The concept of a metabolic cocktail to promote glucose oxidation and reduce free fatty acids to protect the ischemic myocardium dates back to Sodi-Pallares and associates.[22] Early studies with glucose-insulin-potassium (GIK) yielded promising results with a subsequent meta-analysis suggesting that therapy may reduce mortality in acute MI.[23] A prominent Latin American study further suggested that in-hospital mortality was lower among GIK-treated patients in the setting of acute reperfusion (predominately thrombolysis).[24] Despite nearly a half century of study and its low cost and minimal side effect profile, acceptance of the GIK metabolic cocktail in acute MI has been less than forthcoming. The lack of enthusiasm over the use of GIK in acute MI appears to stem from the lack of large randomized trials, controversy over dosing, and a cumbersome mode of delivery.

In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial,[25] acute treatment for at least 24 hours with intravenous insulin, glucose, and potassium until blood sugar was controlled coupled with aggressive subacute treatment with subcutaneous insulin resulted in a 29% relative reduction in 1-year mortality in a cohort of patients with predominately type 2 diabetes. Compared with 43% of control patients, 87% of GIK-treated patients were receiving insulin when they were discharged. Patients with prior insulin use and a low CV risk profile had the most promising results (58% reduction in in-hospital mortality and 52% reduction in 1-year mortality).

In support of the "glucometabolic" hypothesis of reducing CV events in acute MI, recent clinical studies have demonstrated anti-ischemic effects with newer metabolic agents. The alternate strategy of promoting glucose oxidation that appears most promising in clinical studies is the use of partial fatty acid oxidation inhibitors. The 3-ketoacyl-coenzyme thiolase (3-KAT) inhibitors trimetazidine and ranolazine have been shown to reduce myocardial ischemia in both animal and clinical models.[26] These compounds work by switching myocardial metabolism from free fatty acids to glucose oxidation and diminishing the decrease of intracellular ATP which occurs during periods of ischemia.

Role of Lipid-Lowering Agents and Antihypertensives

Lipid-lowering and hypertension trials in type 2 diabetes mellitus have shown significant CV benefit

Table 4
Outcomes Studies Currently in Progress

Study	Main objective	Treatment regimen	Primary endpoint	Secondary endpoint
ADOPT	To evaluate long-term outcomes of TZD monotherapy	Rosiglitazone Metformin Glyburide	Time to monotherapy failure	ß cell function, IS, microalbuminuria, CV surrogates, long-term safety, quality of life
DREAM	To evaluate TZD and ACE inhibitor use in preventing progression of IGT to T2DM	Rosiglitazone + placebo Rosiglitazone + ramipril Ramipril + placebo Placebo alone	Development of diabetes or death from any cause	Adjudicated CV endpoints Microvascular endpoints
RECORD	Evaluate glycemic control and CV events in T2DM	Combination therapy: Metformin, rosiglitazone, SU	Time to combined CV endpoint	Numerous CV and glycemic endpoints
BARI-2D	To compare the glycemic and CV benefits of insulin-sparing (rosiglitazone or metformin) vs insulin-providing (SU or insulin) agents	Rosiglitazone +/- metformin vs SU +/- insulin	Rates of myocardial infarction, ischemic events, angina, quality of life	Pharmacoeconomics of therapy strategy, evaluation of progression and mechanism of vasculopathy
PIOPOD	Evaluate TZD monotherapy to prevent the progression of gestational diabetes-associated insulin resistance to T2DM	Pioglitazone	Development of T2DM	
PROACTIVE	To evaluate TZD therapy in insulin-resistant patients	Pioglitazone	Mortality or cardiovascular events	

ACE, angiotensin-converting enzyme; ADOPT, Avandia Diabetes Outcomes and Progression Trial; BARI-2D, Bypass Angioplasty Revascularization Intervention T2DM; CV, cardiovascular; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; IGT, impaired glucose tolerance; IS, insulin sensitivity; PIOPOD, Pioglitazone for the Prevention of Diabetes; PROACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes; SU, sulfonylureas; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

in persons with longstanding diabetes. Strict glycemic control must, therefore, be coupled with proven therapies to reduce CV events by addressing the atherogenic dyslipidemia and hypertension associated with type 2 diabetes. The "lipid triad" (small, dense low-density lipoprotein [LDL], hypertriglyceridemia, and low HDL levels) associated with the metabolic syndrome and type 2 diabetes is associated with nearly twice the incidence of CV events compared with an isolated LDL alone.[27] Patients with type 2 diabetes have average LDL levels but have an increased number of small, dense LDL particles, which are highly susceptible to oxidative modification and are associated with a 3-fold increase in CV disease.[28] Type 2 diabetes mellitus is associated with increased triglyceride-rich atherogenic particles, which trigger inflammation by activating the transcription factor NF-κB.[29] In addition, low HDL levels deprive patients with type 2 diabetes of maximum protection from reverse cholesterol transport and exposure to potent antioxidants (paroxanase).

Statins and Fibrate Therapy

Multiple lipid-lowering trials with statin and fibrate therapy have shown a marked benefit in reducing CV events in patients with type 2 diabetes (Table 5) that is similar, if not greater, than the extent seen in nondiabetics. The presence of the lipid triad in the 4S study was associated with features of the metabolic syndrome and carried a significant increase in CV events compared with an isolated elevated LDL level.[27] Simvastatin was associated with marked reduction in CV events in both diabetics and patients with impaired glucose tolerance.[30] Diabetics in the Heart Protection Study (HPS) similarly benefited from simvastatin, even in the absence of prior coronary artery disease or high cholesterol levels.[31] Of the nearly 6000 diabetics in HPS, 90% had type 2 diabetes. Similarly, therapy with pravastatin or lovastatin was associated with decreased events in diabetics, especially in those with low HDL levels.[32,33] Recently, a large

Table 5
Lipid-Lowering Agents that Reduce Cardiovascular Risk in Patients with Type 2 Diabetes

Agent	Study	Risk Reduction in Cardiovascular Events
Target low-density lipoprotein		
Simvastatin	4S/HPS	28%-42%
Pravastatin	CARE/LIPID	19%-27%
Lovastatin	AFCAPS/TexCAPS	43%
Atorvastatin	CARDS	Study prematurely halted
Target triglycerides/high-density lipoprotein		
Gemfibrozil	VA-HIT/HHS	24%-71%
Fenofibrate	DAIS	23%
Bezafibrate	BIP	42%

HPS, Heart Protection Study; CARE/LIPID, Cholesterol and Recurrent Events/Long-term Intervention with Pravastatin in Ischemic Disease; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARDS, Collaborative Atorvastatin Diabetes Study; VA-HIT/HHS, Veterans Administration High-Density Lipoprotein Intervention Trial-Helsinki Heart Study; DAIS, Diabetes Atherosclerosis Intervention Study; BIP, Bezafibrate Infarction Prevention study.

trial of low-dose atorvastatin in diabetic patients was halted 2 years prematurely by the data safety monitoring board. In the Collaborative Atorvastatin Diabetes Study (CARDS) of nearly 3000 diabetics who did not meet current European indications for lipid lowering, there was a striking reduction in MI and stroke. Similarly, in the HPS, high-risk diabetic patients benefited from statin therapy even in the absence of significant cholesterol elevations.

In the Veterans Administration High-Density Lipoprotein Intervention Trial (VA-HIT), therapy with gemfibrozil in patients with normal cholesterol levels and low HDL levels resulted in a significant reduction in MI and death.[34] Over half these patients had the metabolic syndrome and benefit was restricted to those with either hyperinsulinemia or overt diabetes. Fibrates raise HDL levels, lower triglycerides, and increase LDL particle size. In post hoc analyses of the Helsinki Heart Study[35] and Bezafibrate Infarction Prevention Trial,[36] patients with the lipid triad had increased CV risk and greater benefit with fibrates. In both trials, CV reduction was seen in the diabetic cohort and patients with hypertriglyceridemia. In the Diabetes Atherosclerosis Intervention Study (DAIS), fenofibrate reduced progression of coronary disease by 40%.[37] Statin therapy may also be effective in treating hypertriglyceridemia in patients with type 2 diabetes. In the Diabetes Atorvastatin Lipid Intervention (DALI) study, both conservative and aggressive atorvastatin therapy (10 mg vs 80 mg) reduced triglycerides 25% to 35% in 217 persons with type 2 diabetes.[38]

Hypoglycemic Agents

The choice of a hypoglycemic agent may also play a role in lipid management. Thiazolidinedione monotherapy is associated with a modest increase in LDL levels (8%-10%), but there is little change in apolipoprotein B levels and a marked shift from a small, dense LDL phenotype to a large, fluffy LDL phenotype.[39] Rosiglitazone in combination with atorvastatin results in a marked shift to a large, fluffy LDL subtype without interfering with the efficacy of statin therapy or increasing side effects.[39] For diabetic patients taking rosiglitazone and 10 to 20 mg of atorvastatin, ≥ 75% of them achieved an LDL of < 100 mg/dL. Thiazolidinediones alone can raise HDL substantially, especially in diabetics with HDL levels below 35 mg/dL.[40] The effect of thiazolidinediones on triglycerides is variable and correlates with the extent of hypertriglyceridemia at baseline. Metformin lowers LDL levels modestly, while raising HDL levels and has a variable effect on triglycerides.[41] Sulfonylureas have only modest, and somewhat variable, effects on lipid levels.

Angiotensin-Converting Enzyme Inhibitors

Similar success at lowering CV event rates have been achieved by aggressive treatment of hypertension in patients with type 2 diabetes mellitus (Table 6). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are clearly preferred for renal protection in diabetic persons with nephropathy.[42] Recently, losartan was also found to have salutary effects on microalbuminuria in normotensive diabetic patients.[43] However, the selective benefit of an individual antihypertensive agent to reduce CV events in patients with type 2 diabetes is less clear. In the Irbesartan Diabetes Nephropathy Trial (IDNT), irbesartan was more effective than amlodipine in reducing progression of renal disease but was not superior in reducing CV events.[44]

Table 6
Antihypertensive Agents That Reduce Cardiovascular Risk in Patients with Type 2 Diabetes

Trial Design	Study	Risk Reduction in Cardiovascular Events
Active therapy vs placebo (ß-blocker, calcium channel blocker, diuretic, ACE inhibitor)	SHEP, HDFP, SYS-EUR, HOPE	25%-62%
Targeted therapy (ß-blocker, ACE inhibitor, calcium channel blocker)	UKPDS, HOT ABCD	Up to 51% with lower target blood pressure
Comparative Trials		
ACE inhibitor vs calcium channel blocker or ß-blocker	ABCD, FACET, CAPP	Up to 49% with ACE inhibitor vs calcium channel blocker
ACE inhibitor or ARB vs calcium channel blocker vs diuretic/ß-blocker	STOP-2, INSIGHT, NORDIL, IDNT	No difference among agents
ARB vs ß-blocker	LIFE	24% with ARB
Diuretic vs ACE inhibitor vs calcium channel blocker Diuretic vs ß-blocker	ALLHAT UKPDS	No difference among agents

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SHEP, Systolic Hypertension in the Elderly Program; HDFP, Hypertension Detection and Follow-up Program; SYS-EUR, Multicentre Trial on Treatment of Isolated Systolic Hypertension; HOPE, Heart Outcome Prevention Evaluation; UKPDS, United Kingdom Prospective Diabetes Study; HOT, Hypertension Optimal Therapy; ABCD, Appropriate Blood Pressure Control in Diabetes; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; CAPP, Captopril Prevention Project; STOP-2, Swedish Trial in Old Patients with Hypertension; INSIGHT, Intervention as a Goal in Hypertension Treatment; NORDIL, Nordic Diltiazem study; IDNT, Irbesartan Diabetes Nephropathy Trial; LIFE, Losartan Intervention for End Point reduction in hypertension study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

Earlier trials[45-47] had suggested a selective CV benefit of ACE inhibitors over diuretics and calcium channel blockers in patients with type 2 diabetes. Similarly, the recent Losartan Intervention For Endpoint reduction in hypertension study (LIFE)[48] suggested a relative CV benefit (primarily a reduction in stroke) with the ARB losartan over the ß-blocker atenolol in type 2 diabetic patients with hypertension and left ventricular hypertrophy. In UKPDS, however, ACE inhibitors and ß-blockers were found to be equally effective,[49] although persons taking ß-blockers gained more weight and required more glucose-lowering agents. In the Hypertension Optimal Treatment (HOT) study, aggressive diastolic blood pressure lowering to a target of 80 mm Hg versus 90 mm Hg with a dihydropyridine calcium channel blocker–based regimen resulted in 51% fewer CV events in the diabetic cohort.[50] Similarly, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed no difference in CV or renal outcomes in over 10,000 diabetic patients randomized to chlorthalidone, amlodipine, or lisinopril.[51]

The thiazide diuretic was, however, associated with an increased risk of type 2 diabetes developing in the ALLHAT population over 5 years. ß-Blockers similarly worsen insulin resistance, which may have contributed to the increased risk of type 2 diabetes developing in the atenolol arm of the LIFE trial. Conversely, ACE inhibitors have been shown to improve insulin sensitivity and decrease the development of type 2 diabetes.[52] Thus, the major emphasis should first be on reaching appropriate blood pressure targets in patients with type 2 diabetes, which frequently requires polypharmacy with up to 3 or 4 agents. Recent data from the National Health and Nutrition Examination Survey (NHANES) registry suggests that < 15% of diabetic patients meet JNC 6 blood pressure targets.[53] Finally, the new guidelines established by the Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure stress the use of aggressive combination drug therapy to achieve blood pressure goals in high risk patients.[54]

Lifestyle Modifications

Measures to improve CV outcomes in diabetics must also begin with aggressive lifestyle modifications concentrating on diet, weight loss, and exercise. Regular exercise alone can decrease the development of type 2 diabetes, and a regular walking program was shown to reduce total mortality 42% in patients with type 2 diabetes mellitus.[55] Exercise 5 times weekly for 30 minutes com-

bined with modest weight loss substantially reduced insulin resistance as witnessed by the greater than 50% reduction in the development of type 2 diabetes in high-risk glucose intolerant persons in the Diabetic Prevention Project Group.[56] A comprehensive Finnish trial of lifestyle modifications yielded similar results.[57] The effects of aggressive lifestyle modifications on improving insulin sensitivity were similar, if not greater, than the results seen with metformin, thiazolidinediones, or α-glucosidases.[56,58,59] Recent evidence suggests that therapy to reduce glucose absorption and decrease postprandial hyperglycemia with acarbose not only decreased the incidence of new-onset type 2 diabetes but was associated with a reduction in CV events.[60]

The results of a comprehensive multifactorial intervention trial to reduce both microvascular and macrovascular events in patients with type 2 diabetes and microalbuminuria were especially gratifying.[61] Intensive stepwise intervention with behavioral and lifestyle modifications coupled with pharmacologic therapy targeting hypertension, dyslipidemia, and microalbuminuria (ACE inhibitor use), as well as secondary CV protection with aspirin, resulted in dramatic reductions (approximately 50%) in both microvascular and macrovascular events compared with conventional therapy. The mean HbA_{1c} was reduced 0.7% in the intensive arm, compared with the control arm. Sixty percent of intensively treated patients were receiving insulin (median dose 62 units). Insulin sensitizing agents were, however, not employed in this study.

Maintaining strict glycemic control is an integral part of the global strategy to prevent both microvascular and macrovascular events in patients with type 2 diabetes.

Future Directions and Conclusions

Recent evidence suggests an important role for cell surface receptors for AGE (RAGE) in the progression of established atherosclerosis in patients with type 2 diabetes.[62] Soluble RAGE was shown to halt the progression of established atherosclerosis in a murine model, while qualitatively improving plaque composition and inflammation, which may lead to "plaque stabilization." While awaiting the results of ongoing trials with current antidiabetic therapies and future studies with new modalities, we must vigilantly address strategies proven to reduce CV complications. Treating CV risk factors goals targeted by national guidelines (blood pressure 130/80 mm Hg in JNC 7, and perhaps lower in the setting of renal disease or coronary artery disease), adhering to NCEP III lipid guidelines, and implementing aggressive nonpharmacologic lifestyle modifications are of paramount importance. Appropriate use of aspirin is equally important in both primary

Main Points

- Insulin, sulfonylurea, and short-acting insulin secretagogues have little to no effect on improving insulin sensitivity and thus, unlike the insulin sensitizers (metformin and thiazolidinediones), have little effect on the proinflammatory, prothrombotic, and oxidative consequences of insulin resistance.
- In the Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) I and II trials, metformin or thiazolidinedione use was associated with fewer CV events than insulin or sulfonylurea therapy in over 3000 diabetics with acute coronary syndromes.
- Rosiglitazone in combination with atorvastatin results in a marked shift to a large, fluffy LDL subtype without interfering with the efficacy of statin therapy or increasing side effects.
- The thiazide diuretics were associated with an increased risk of developing type 2 diabetes developing in the ALLHAT population over 5 years.
- Fibrates raise high-density lipoprotein levels, lower triglycerides, and increase low-density lipoprotein particle size.
- Aggressive treatment of hypertension (eg, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, usually in combination with other agents) lowers cardiovascular events in patients with type 2 diabetes.
- In addition to strict glycemic control and pharmacologic therapy, lifestyle modification (eg, diet, weight loss, and exercise) provides a cornerstone for the management of type 2 diabetes mellitus.

and secondary prevention in diabetics and nondiabetic subjects.[63] Maintaining strict glycemic control is an integral part of the global strategy to prevent both microvascular and macrovascular events in patients with type 2 diabetes. Preliminary data suggest that targeting insulin resistance may yield important advances in reducing macrovascular events. ■

References

1. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care*. 1979;2:120-126.
2. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001;286:1195-1200.
3. 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.
4. Bierman EL. George Lyman Duff Memorial Lecture. Atherogenesis in diabetes. *Arterioscler Thromb*. 1992;12:647-656.
5. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. *Diabetes*. 1995;44:1386-1391.
6. Varo N, Vincent D, Libby P, et al. Elevated plasma levels of the atherogenic mediator soluble CD40 ligand in diabetic patients. *Circulation*. 2003;107:2664-2669.
7. Libby P, Plutzky J. Diabetic macrovascular disease: the glucose paradox? *Circulation*. 2002;106:2760-2763.
8. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
9. Knatterud GL, Klimt CR, Levin ME, et al. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII. Mortality and selected nonfatal events with insulin treatment. *JAMA*. 1978;240:37-42.
10. 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.
11. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1999;33:119-124.
12. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865.
13. McGuire DK, Newby LK, Bapkar MV, Moliterno DJ, et al. Diabetes doubles the risk of death after acute coronary syndrome: Insights from SYMPHONY: A large international trial. *JACC*. 2001;37:372A.
14. Sauer WH, Berlin JA, Kimmel SE. Thiazolidinediones and prevention of myocardial infarction with type 2 diabetes. *Circulation*. 2002;106:562.
15. Marx N, Libby P, Plutzky J. Peroxisome proliferator-activated receptors (PPARs) and their role in the vessel wall: possible mediators of cardiovascular risk? *J Cardiovasc Risk*. 2001;8:203-210.
16. Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med*. 2001;134:61-71.
17. Yue T, Chen J, Boa W, Narayanan PK, et al. In vivo myocardial protection from ischemia/reperfusion injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. *Circulation*. 2001;104:2588-2594.
18. Shiomi T, Tsutsui H, Hayashidani S, et al. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation*. 2002;106:3126-3132.
19. Inzucchi S. Oral antihyperglycemic therapy for type 2 diabetes. *JAMA*. 2002;287:360-376.
20. UK Prospective Diabetes Study (UKPDS) Group. Overview of 6 years' therapy of type 2 diabetes: a progressive disease. *Diabetes*. 1995;44:1249-1258.
21. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000;283:1695-1702.
22. Sodi-Pallares D, Testelli MR, Fishleder BL, et al. Effects of an intravenous infusion of a potassium-insulin-glucose solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *Am J Cardiol*. 1962;9:166-181.
23. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation*. 1997;1:107-114.
24. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction. The ECLA glucose-insulin-potassium pilot trial. *Circulation* 1998;98:2227-2234.
25. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57-65.
26. Conti R. Partial fatty acid oxidation (pFOX) inhibition: A new therapy for chronic stable angina. *Clin Cardiol*. 2003;26:161-162.
27. Ballantyne CM, Olson AG, Cook TJ, et al. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation*. 2001;104:3046-3051.
28. Lamarche B, St-Pierre AC, Ruel IL, et al. A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. *Can J Cardiol*. 2001;17:859-865.
29. Dichtl W, Nilsson L, Goncalves I, et al. Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells. *Circ Res*. 1999;84:1085-1094.
30. Herman WH, Alexander CM, Cook JR, et al. Effect of simvastatin treatment on cardiovascular resources utilization in impaired fasting glucose and diabetes; findings from the Scandinavian Simvastatin Survival Study. *Diabetes Care*. 1999;22:1771-1778.
31. 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.
32. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med*. 1996;335:1001-1009.
33. Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary heart events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*. 2000;97:1453-1460.
34. Robins SJ, Collins D, Witters JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events; VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585-1591.
35. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation*. 1992;85:37-45.
36. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease; the Bezafibrate Infarction Prevention (BIP) Study. *Circulation*. 2000;102:21-27.
37. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;357:905-910.
38. The Diabetes Atorvastatin Lipid Intervention (DALI) Study Group. The effects of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: The DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. *Diabetes Care*. 2001;24:1335.
39. Freed MI, Ratner R, Marcovina SM, et al. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol*. 2002;90:947-952.
40. Schaefer E, Gould E. Rosiglitazone increases high-density lipoprotein cholesterol levels in patients with type 2 diabetes. *J Am Coll Cardiol*. 2003;316A.
41. Kirpichnikov D, McFarlane S, Sowers JR. Metformin: An update. *Ann Intern Med*. 2002;137:25-33.
42. 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.

43. Zandbergen A, Baggen M, Lamberts SN, et al. Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus. A randomized clinical trial. *Ann Intern Med*. 2003;139:90-96.
44. 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.
45. 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 (CAPP) randomised trial. *Lancet*. 1999;353:611-616.
46. 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;338:645-652.
47. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care*. 1998;21:596-603.
48. Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Invention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:1004-1010.
49. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Study Group. *BMJ*. 1998;317:703-713.
50. 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) randomized trial. HOT Study Group. *Lancet*. 1998;351:1755-1762.
51. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2991.
52. Yusuf S, Gerstein H. Hoggwerf B, et al. HOPE Study Investigators. Ramipril and the development of diabetes. *JAMA*. 2001;286:1882-1885.
53. 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.
54. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.
55. Tanasescu M, Leitzmann M, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation*. 2003;107:2435-2439.
56. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;347:709-715.
57. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-1350.
58. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes*. 2002; 51:2796-2803.
59. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes: the STOP-NIDDM randomised trial. *Lancet*. 2002; 359:2072-2077.
60. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA*. 2003;290:486-494.
61. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:393-403.
62. Bucciarelli LG, Wendt T, Qu W, et al. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. *Circulation*. 2002;106:2827-2835.
63. Antiplatelet Trialist's Collaboration. Collaborative overview of randomized trials of antiplatelet therapy: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81-106.