

Cardiovascular Complications of Diabetes: Prevention and Management

Alan J. Garber, MD, PhD

Professor of Medicine, Biochemistry and Molecular Biology
and Molecular and Cellular Biology
Baylor College of Medicine
Chief of Endocrinology, Diabetes and Metabolism
The Methodist Hospital
Houston, Texas

Cardiovascular (CV) complications are by far the most prevalent in patients with type 2 diabetes and the principal cause of mortality. Renal complications of type 1 diabetes were the principal cause of death. However, with the advent of dialysis and renal transplantation and because of further increases caused by such management techniques on the already accelerated atherosclerosis of type 1 diabetes patients, CV complications have now become the principal cause of morbidity and mortality. For successful prevention of CV complications in diabetes, clinicians should therefore pay particular attention to the means of attaining goals for the management of established traditional as well as nontraditional CV risk factors. For the most part, such management has been proven to reduce CV events in patients with diabetes, particularly type 2 diabetes.

Causation of accelerated atherosclerosis in diabetes is multifactorial and clearly begins years or even decades prior to the diagnosis of type 2 diabetes. Atherosclerosis in diabetic patients is characterized by several factors, including an increase in rates of mortality following coronary events, in thrombosis and restenosis following invasive revascularization procedures, and in coronary event recurrence, and by the need for broad multitherapeutic intervention that goes well beyond maintenance of glycemic control. Diabetes per se as a risk factor for coronary disease increases the risk of atherosclerotic events 2- to 4-fold, depending on gender and ethnic differences. Heightened degrees of cardiovascular (CV) risk are produced in diabetic patients compared with nondiabetic patients by traditional CV risk factors such as cigarette smoking and hypertension. Since many patients with type 2 diabetes have a plethora of tradi-

KEY POINT

Diabetes appears to act as an amplifier of CV risk, multiplying the impact of underlying risk factors.

tional as well as nontraditional CV risk factors, a systematic and rigorous normalization of such risk factors may lead to a substantial reduction if not normalization of rates of CV disease in patients.

INCIDENCE AND PREVALENCE OF CV COMPLICATIONS

CV complications in patients with type 2 diabetes

appear to have had their genesis long before the diagnosis of this disease. In the United Kingdom Prospective Diabetes Study (UKPDS), ~20% to 25% of newly diagnosed patients with type 2 diabetes had evidence of atherosclerosis (1). In the Bedford Diabetes Study, Jarrett et al (2) noted that newly diagnosed patients with type 2 diabetes had virtually identical CV morbidity and mortality rates as patients with long-established type 2 diabetes. The findings may reflect an important element of insulin resistance in the pathogenesis of this condition. Such resistance begins one or more decades before diagnosis, and may be associated with a multifactorial, high-risk CV state known as the *metabolic syndrome*.

Although a definitive characterization of the presence or absence of insulin resistance can be provided only by direct tests of insulin-mediated glucose disposal, such as insulin clamp techniques, such technology is impractical in the routine clinical setting. Therefore, a number of indirect diagnostic criteria have been proposed that seek to improve the diagnostic accuracy and recognition of patients with insulin resistance, especially with high-risk CV states such as the *metabolic syndrome*. A number of discriminators predict the presence of insulin resistance, such as an atherogenic dyslipidemia, hyperuricemia, the presence of central obesity, and conditions often associated with and perhaps resulting from insulin resistance, such as polycystic ovary syndrome. The diagnostic

criteria suggested by the National Cholesterol Education Program (NCEP) of the National Heart, Lung, and Blood Institute (**Table I**) provide a useful tool for routine clinical diagnostic assessments of high-risk CV states (3). The presence of 3 of the 5 diagnostic elements is sufficient for a diagnosis of the *metabolic syndrome*. The diagnostic points often become action points for therapeutic intervention and will be used in this article as part of the rationale for managing lipid disorders in patients with diabetes.

Overall rates of CV mortality are increased some 2- to 4-fold in men and women respectively with diabetes as compared with their nondiabetic cohorts (4). Precise risk ratios vary from study to study and with the ethnicity and gender of subjects. In all circumstances, diabetes clearly confers additional CV morbidity and mortality across all ethnic backgrounds and genders.

Ultimately, ~ three fourths of all patients with diabetes will eventually die as a result of CV complications of diabetes. In the Multiple Risk Factor Intervention Trial (5), diabetes as a risk factor for coronary artery disease had the impact of at least 2 and up to 3 traditional CV risk factors, including hypercholesterolemia, hypertension, and cigarette smoking (5). The risk of CV events in patients with type 2 diabetes ranges from 3% to 6% per year depending on the study cited in a broad range of populations (6). For example, in a study conducted in Finland, patients with diabetes but

TABLE I.

NCEP CRITERIA FOR THE METABOLIC SYNDROME—3 OF 5 SUFFICIENT FOR DIAGNOSIS

1. Abdominal obesity	Waist \geq 40" (male) Waist \geq 35" (female)
2. Triglycerides	>150 mg/dL
3. HDL cholesterol	<40 mg/dL (males) <50 mg/dL (females)
4. Hypertension	>130/85 mm Hg
5. Impaired fasting glucose	\geq 110 mg/dL

HDL = high-density lipoprotein; NCEP = National Cholesterol Education Program.

without known coronary artery disease had a 3-fold increase in CV risk compared with nondiabetic matched subjects. Worse yet, diabetic patients with known coronary disease had an increased risk of coronary disease when matched to nondiabetic patients with known coronary disease (7). Thus, diabetes appears to act as an amplifier of CV risk, multiplying the impact of the underlying risk factors in patients.

Although the histopathology of atherosclerotic lesions in patients with diabetes appears similar if not identical compared with nondiabetic patients, the geographic distribution of these lesions within the coronary circulation seems to be somewhat different. Patients with diabetes have a greater proportion of distal arterial disease, rendering invasive revascularization more difficult and less satisfactory, compared with nondiabetic patients. There is also an increased incidence of left main coronary artery disease or its equivalent, namely critical lesions at the proximal left anterior descending and circumflex branches of the left coronary artery. It should be noted, however, that diabetic patients taking insulin therapy in the Bypass Angioplasty Revascularization Investigation (BARI 1) Trial (8) appeared to have an increased proportion of fibromuscular transformation of lipid-rich coronary plaques into less lipid filled but more highly cellular and diffusely proliferative atherosclerotic disease, an observation being further investigated in the BARI 2 study.

MANAGEMENT OF CLINICALLY SYMPTOMATIC CORONARY ARTERY DISEASE

Invasive surgical or percutaneous transluminal revascularization procedures in patients with diabetes have been carefully investigated in multiple trials. In general, patients with diabetes have an increased rate of restenosis following percutaneous transluminal angioplasty. In the BARI 1 Trial, mortality in diabetic patients treated by coronary angioplasty was double that seen in patients treated by coronary artery bypass surgery, provided that such bypass procedures included left internal mammary artery implantation into the left anterior descending coronary artery. However, in patients

not receiving internal mammary implantation but merely a coronary artery vein graft bypass, the surgery revealed no advantage over angioplasty. The finding in BARI 1 has proven to be highly controversial and has prompted BARI 2, an ongoing follow-up successor study, in which patients with diabetes will be randomized to 1 of 3 treatment programs; these include angioplasty aided by stents and modern technology for reduction of restenosis, and coronary artery bypass surgery with internal mammary artery implantation. A third treatment arm of intensive medical management only will also be studied. All of the patients will be randomized to an insulin sensitizing treatment arm using rosiglitazone and metformin, and compared with an insulin-providing arm using sulfonylureas and insulin.

Investigations have provided insight into vein graft restenosis and postangioplasty restenosis through the use of glycoprotein IIb/IIIa inhibitors following angioplasty inhibitors, such as abciximab. Abciximab has been shown in randomized controlled trials, such as EPISTENT (Evaluation of IIb/IIIa Platelet Inhibition for Stenting), to substantially eliminate the excess restenosis of postangioplasty in diabetic patients (9). These inhibitors are short-lived treatments given only immediately after angioplasty. However, abciximab itself seems to have more than antiplatelet activity; there appears to be some activity with respect to suppression of vascular smooth muscle proliferation, which may account for the prolonged near-normalization of restenosis rates as seen in diabetic patients in EPISTENT. Most of the early restenosis in diabetic patients, as well as excess atherosclerosis, derives from an increased clotting tendency characterized by shortened platelet survival time and increased rates of thrombotic, coronary, and cerebrovascular events.

In general, antiplatelet maneuvers have been successful in diabetic patients with respect to improvements of CV and cerebrovascular risk. Treatment such as aspirin has been well documented in multiple trials to reduce CV risk by 20% to 25% (10). In patients failing aspirin or who are aspirin intolerant, adenosine diphosphate receptor antagonists including clopidogrel may add additional CV and cerebrovascular protection.

MANAGEMENT OF CV RISK FACTORS

Lipid Regulation

Patients with type 2 diabetes frequently have an atherogenic dyslipidemia characterized by low high-density lipoprotein (HDL) cholesterol levels (<40 mg/dL in males or <50 mg/dL in females) and elevated triglyceride levels in the fasting state (>150 mg/dL). As a consequence of the underlying insulin resistance of these patients, the hypertriglyceridemia is frequently associated with a shift in the profile of low-density lipoprotein (LDL) particle size distribution toward a smaller and more dense LDL particle (phenotype B LDL profile) of increased atherogenic risk. Austin et al (11) have suggested that such a phenotype is associated with nearly triple the atherogenic risk of phenotype A—a larger, more buoyant LDL particle. Oftentimes LDL mass is less than might be expected for such overweight, sedentary patients as seen with type 2 diabetes, which has led to the misconception that these patients do not require lipid regulation therapy for primary prevention or management of existing coronary disease. However, it is now clear, based on numerous randomized, controlled, prospective, interventional trials that lipid regulation is a key component in the management of CV disease and its prevention in these patients (Table II).

The UKPDS showed that LDL cholesterol was the major risk predictor for coronary disease in

patients with type 2 diabetes. The key role of LDL cholesterol in the genesis and progression of atherosclerosis was established by observations in a number of important clinical trials. The trials began with a retrospective analysis of a small cohort of 202 diabetic patients contained in a much larger patient population studied in the Scandinavian Simvastatin Survival Study or 4S trial (12). In these mildly diabetic patients with marked hypercholesterolemia (LDL cholesterol 187 mg/dL), intervention with simvastatin reduced CV recurrence ~54%. This reduction was numerically greater than that seen in the nondiabetic population of the 4S trial. Events in diabetes were not a pre-specified endpoint in this trial; additional studies

KEY POINT

The Heart Protection Study clearly suggests that diabetic patients should receive a statin as initial therapy for the prevention and treatment of coronary disease.

are required to support this potentially hypothesis-generating observation.

In the Cholesterol and Recurrent Events Study (CARE), 586 patients with type 2 diabetes

TABLE II.

LIPID REGULATION IN DIABETES

Step 1	Diet + Exercise + Diabetes Control
Step 2	LDL cholesterol \geq 100 mg/dL or LDL cholesterol <100 mg/dL + coronary equivalent Action: Add statin
Step 3	HDL cholesterol <40 mg/dL (males) HDL cholesterol <50 mg/dL (females) Action: Add niacin
	Or
Step 4	Triglycerides >1000 mg/dL Action: Consider insulin or fish oils

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

were enrolled and randomized to either pravastatin or placebo (13). After 5 years of therapy, these patients had 27% fewer recurring coronary events when treated with pravastatin than when randomized to placebo. Patients in CARE had much more modest levels of LDL cholesterol (139 mg/dL) and had a much higher prevalence of aspirin use or prior revascularization procedures. As in the 4S trial, the diabetic patients in CARE showed a numerically greater therapeutic benefit from LDL lowering with a statin than did the nondiabetic patients receiving statin therapy. The attained LDL goal on average in this study was 98 mg/dL; therefore, this presents an important experimental basis for the current LDL target of <100 mg/dL in patients with diabetes. To ascertain whether a reduction of CV events is also accompanied by a reduction in CV and total mortality, a much larger trial, Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), which consisted of ~9000 subjects, was conducted by the Australia and New Zealand Heart Association (14). By the time LIPID was conducted, there was considerably more interest from patients in statin therapy. Thus, the control group was partially treated with resins or pravastatin compared with the experimental group, which was much more aggressively treated with pravastatin. A significant reduction of CV and total mortality was seen in the aggressively treated group when compared with less aggressive interventional therapy (14). In the diabetic cohort, the primary endpoints showed no difference with aggressive intervention with pravastatin compared with the partially treated placebo control group. However, an expanded endpoint using both fatal and nonfatal coronary disease as well as hospitalizations for revascularization procedures whether by bypass surgery or angioplasty, did show a significant treatment benefit with pravastatin in diabetic patients compared with partially treated placebo control patients. The extent of the benefit with regard to the expanded endpoint was numerically greater than that seen in nondiabetic patients. In all of these trials, the residual coronary event rate in the treated diabetic cohorts with statin therapies exceeded the rate of coronary events in the nondiabetic cohorts after treatment.

The question remains as to how low LDL cholesterol should be dropped, or what treatment targets should be for diabetes patients who have a greatly increased risk of coronary disease and an abnormally atherogenic LDL particle. This issue has been partially addressed by the recently published findings of the Heart Protection Study, in which ~20,500 high-risk patients were randomized to intervention with simvastatin (40 mg/day) or to placebo. However, as with other more recent statin trials, placebo-controlled patients were partially treated owing to the publicity surrounding cholesterol and coronary disease. A broad range of LDL cholesterol levels was studied at the time of randomization, including a substantial number of patients randomized with LDL cholesterol levels of 100 mg/dL or less (15). In those patients, significant treatment benefits with simvastatin intervention were seen even at such low LDL cholesterol levels at the time of randomization. Attained LDL cholesterol in this subpopulation was <80 mg/dL. Similar findings in a smaller and less robust study (Post-Coronary Artery Bypass Graft) suggest that very low LDL cholesterol goals in especially high-risk patients, such as those with diabetes (with or without known coronary disease), are likely to be associated with greater treatment benefit than LDL cholesterol levels of 100 mg/dL as a treatment goal (16).

In the NCEP, diabetic patients with LDL cholesterol greater than 130 mg/dL were strongly encouraged to receive 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor therapy to target an LDL cholesterol of <100 mg/dL. In patients with LDL <100 mg/dL, such therapy was not recommended and hygienic measures such as diet and exercise were advocated as the backbone of therapy. For intermediate levels of LDL cholesterol (100 to 129 mg/dL), statin therapy was considered discretionary according to the judgment of the medical practitioner. However, the results of the Heart Protection Study clearly suggest that regardless of LDL cholesterol levels, diabetic patients should receive a statin as initial therapy for treatment of known coronary disease and likely for its prevention.

For patients with established coronary dis-

ease, the likely target for LDL regulation may well be <80 mg/dL rather than <100 mg/dL as previously recommended. Attainment of such very low LDL cholesterol levels may be difficult even with highly potent statins such as atorvastatin. Additionally, as the dose of the statin increases, the risk of adverse side effects, especially myopathy, increases. Accordingly, combination therapy with a recently released cholesterol absorption inhibitor, ezetimibe, may be considered in such patients. Ezetimibe uniquely inhibits the absorption of cholesterol and other sterols at the intestinal brush border. Its mechanism of action is different from bile acid binding resins. As monotherapy, ezetimibe lowers LDL cholesterol ~15% to 20%. However, ezetimibe in combination with a statin produces an incremental 15% to 20% further reduction in LDL cholesterol (17). Thus, ezetimibe in combination with low-dose simvastatin (10 mg) produces an LDL reduction greater than that seen for 40 mg to 80 mg of simvastatin. Because of the rather flat dose-response curve of statins, it therefore may be therapeutically more efficacious to add a second agent (ezetimibe) to a low-dose statin while minimizing the potential for adverse effects than to fully titrate the statin to the maximum possible dose.

Additional complications of statin therapy derive from the metabolism of all but one of these molecules through cytochrome P450 3A4. With the exception of pravastatin, all other HMG-CoA inhibitors require the activity of 3A4 for clearance. Since more than half the drugs whose metabolism has been documented are indeed metabolized by 3A4, the potential for complex, adverse drug interactions through this particular hepatic cytochrome is clearly present and has been documented for multiple other agents in the past. The US Food and Drug Administration (FDA) has recently mandated a reduction in dosage of simvastatin approved for combination with some other agents metabolized through 3A4, such as calcium channel blockers and other lipid regulating compounds, including gemfibrozil and nicotinic acid. Thus, care should be taken when using multiple drugs passing through 3A4 together to minimize the risk for cardiac and skeletal muscle toxicity with this class of compounds.

Having regulated LDL cholesterol by appropriate therapy with HMG-CoA inhibitors alone or aided by additional agents such as ezetimibe or bile acid binding resins, attention should then be placed on regulation of HDL cholesterol and triglycerides. Low levels of HDL cholesterol and elevated triglyceride levels are a frequent concomitant of type 2 diabetes. Type 1 diabetes on the other hand is generally associated with normal to increased levels of HDL cholesterol. In such patients, elevated triglyceride levels rarely, if ever, occur except as the result of poorly controlled, chronic hyperglycemia. Therefore, in type 1 patients, the management of disorders of HDL and triglyceride metabolism should focus on diabetes management per se. In contrast, patients with type 2 diabetes often require pharmacologic regulation of both HDL cholesterol and triglyceride levels. In diabetic patients with HDL cholesterol levels <40 mg/dL, weight reduction and regular daily exercise are a mainstay of therapy. Oftentimes, diabetic patients have difficulty with aerobic exercise, but such exercise is essential for increasing levels of HDL cholesterol.

Marked hypertriglyceridemia in patients with diabetes most likely reflects a failure of diabetes control. It may be the result of excess alcohol intake, excess carbohydrate intake, or poor diabetes management as judged by elevated glycated hemoglobin A (HbA_{1c}) levels. In patients in whom dietary and alcohol compliance is obtained, persistent hypertriglyceridemia is a mandate for initiation of insulin therapy since oral agents are generally less effective in controlling hypertriglyceridemia than insulin. The use of insulin in diabetic patients with marked hypertriglyceridemia (>1000 mg/dL) is essential to reduce the risk of chylomicron-associated pancreatitis. Oftentimes, intensive insulin management using analog insulin preprandially and analog insulin at bedtime will be required to obtain the degree of strict diabetes control necessary to improve triglyceride levels in this patient population. However, triglycerides will not completely normalize on insulin alone and additional lipid-regulating therapy, such as fibric acid derivatives, may be necessary. Additionally, fish oil capsules may be used as a dietary supplement to improve hypertriglyceridemia in patients with diabetes. These

agents may be expected to reduce triglyceride levels as much as 300 to 500 mg/dL but may not be sufficient to normalize levels.

Pharmacologic therapy to raise HDL cholesterol is available either in the form of nicotinic acid or a fibric acid derivative. Although nicotinic acid is in general more efficacious in raising HDL cholesterol than fibric acid derivatives, its use may be complicated by a worsening state of insulin resistance and diabetes control. Some authors have regarded nicotinic acid as relatively contraindicated in diabetic patients. Nonetheless, nicotinic acid, particularly the extended-release preparation, can clearly be used in diabetic patients with the hyperglycemia potentially resulting from its use controlled by aggressive interventions.

Fibric acid derivatives. Fibrates are somewhat less satisfying in terms of their ability to raise HDL cholesterol but clearly more effective in reducing triglyceride levels, which may ultimately prove to be an important element for the correction of the low HDL cholesterol in patients with type 2 diabetes. Patients with isolated low HDL cholesterol—even in the presence of normal triglyceride levels—are often insulin-resistant. Thus, attention should be paid to the management of such an insulin-resistant state.

Two fibric acid derivatives are currently available for use in the United States—gemfibrozil and fenofibrate. Other fibric acid derivatives, such as bezafibrate*, are available in Europe but are not recommended. Of all the fibric acid derivatives studied thus far, only gemfibrozil has been proven effective for both primary and secondary CV prevention as documented in the Helsinki Heart Study (18) and the Veterans Affairs HDL Intervention Trial (VA-HIT) (19). Prior concerns regarding the safety of fibric acid derivatives with respect to the possibility of increased mortality, as raised by clofibrate in the WHO Clofibrate Trial (20), have not been seen with gemfibrozil. Thus, its use appears to be safe and effective for patients with diabetes, as shown in the VA-HIT of >2500 patients in whom 25% were diabetic. These patients had an HDL at

the time of randomization of 32 mg/dL, a triglyceride of >160 mg/dL, and an LDL cholesterol level of 111 mg/dL. After 5 years of therapy with gemfibrozil, diabetic patients noted a 24% reduction of fatal and nonfatal myocardial infarctions compared with those diabetic patients administered placebos. Investigators attributed this therapeutic benefit of gemfibrozil to a 6% increase in HDL cholesterol levels from 32 to 34 mg/dL. It should be noted, however, that triglyceride levels fell ~30 mg/dL from 160 to 130 mg/dL. A decline in triglyceride levels in this range would be expected to shift LDL particle size from a small, dense atherogenic LDL particle toward a more buoyant, less atherogenic LDL particle. This effect, although theoretical and not measured in this trial, may partially explain the therapeutic benefit of gemfibrozil.

Regardless of the mechanism, it seems clear that gemfibrozil is a reasonable therapeutic agent for patients with diabetes, especially those with known coronary disease who have either low HDL cholesterol or elevated triglyceride levels or both. It may be used in combination with statin therapy for patients with mixed dyslipidemias. However, both gemfibrozil and statins have been reported to cause myopathy as an adverse effect. As noted earlier, simvastatin has been limited to the 10-mg dose with nicotinic acid, and perhaps with fibrates as well; therefore, limited doses of simvastatin or other statins should be used. On the other hand, some studies have suggested greater safety with pravastatin in combination with fibric acid derivatives. Certainly such improved safety margins appear evident with pravastatin in combination with nicotinic acid.

In contrast to gemfibrozil, no other fibric acid derivative has thus far demonstrated CV risk reduction. Bezafibrate failed to produce a significant treatment benefit in the Bezafibrate Infarction Prevention Trial (BIP) (21); fenofibrate failed in the Diabetes Atherosclerosis Intervention Study (DAIS) (22). It should be noted, however, that fenofibrate is more efficacious than gemfibrozil in reducing triglyceride and LDL cholesterol levels. Whether or not the effect of gemfibrozil with regard to proven CV risk reduction is a class effect remains an open question in light of the failure of bezafi-

* Not FDA approved.

brate. Thus, extrapolation of a gemfibrozil-like benefit to be anticipated from fenofibrate seems unreasonable at the present time.

Nicotinic acid. Nicotinic acid may also be useful for raising HDL cholesterol, although less useful in lowering triglyceride levels. Much enthusiasm exists for the use of nicotinic acid, even in diabetic patients, owing to its relatively potent effect as an agonist of HDL cholesterol. Although nicotinic acid tends to initially reduce levels of fatty acids, this is followed by a rebound increase in free fatty acids, which may account for the worsening insulin resistance associated with this agent. Increases in HDL cholesterol of 2 to 3 times that seen with fibric acid derivatives are commonplace. However, nicotinic acid is also difficult to use, requiring a slow, progressive titration to minimize the short-term adverse effects of flushing, pruritus, and hypotension. Because of these short-term side effects, together with the longer term potential for drug interactions with statin therapy, nicotinic acid should be titrated with care, especially in diabetic patients already taking statin therapy (which should be virtually all diabetic patients as we presently understand the benefits of statin therapy in this patient population). Only pravastatin is specifically indicated for use with nicotinic acid. Alternatively, long-acting preparations of niacin have far fewer side effects, require less titration, and have improved patient compliance. A combination product of lovastatin plus long-acting nicotinic acid is now available. This agent produces striking effects on LDL and HDL cholesterol and may become a first-line agent for diabetic patients with the *metabolic syndrome*.

Statin therapy. Patients with type 2 diabetes will likely require one or more lipid regulating agents as part of a comprehensive CV risk reduction program. In almost all instances, a statin should be used in patients with diabetes—certainly in those patients with diabetes and known atherosclerotic coronary artery disease or its equivalent where a statin is overwhelmingly indicated. In patients without known coronary disease but who have diabetes, statin therapy is also clearly indicated as long as

LDL cholesterol levels are >100 mg/dL. Statin therapy may be considered optional in diabetic patients with LDL cholesterols between 80 and 100 mg/dL in the absence of known coronary disease; however, statins are clearly beneficial in all diabetic patients. Owing to the presence of residual atherogenic dyslipidemia, such as low HDL cholesterol or elevated triglyceride levels, additional therapeutic agents such as fibric acid derivatives or nicotinic acid may be necessary. Such agents should be used with care in combination with statins. Appropriate dosage modifications or medication alterations may be necessary to avoid symptomatic complications of multidrug interactions, especially myopathy with creatine kinase elevations.

Blood Pressure Regulation

Hypertension is as important or perhaps a more important risk factor for the development of complications of diabetes as is hyperglycemia. This is particularly true for microvascular complications such as retinopathy and nephropathy. In multi-center trials, such as the Diabetes Control and Complications Trial (DCCT) and the UKPDS, each 1% reduction of HbA_{1c} levels produced a 25% to 35% reduction in microvascular complications. On the other hand, a 5-mm Hg reduction in diastolic pressure produced a 37% reduction in microvascular complications in the UKPDS (23). The impact of hyperglycemia seems to be more important early in the course of the development and progression of microvascular complications. Correction of hypertension, while important early in the prevention of complications, seems to have an even greater impact as microvascular complications progress. For example, aggressive blood pressure (BP) regulation becomes very important after overt nephropathy becomes well established. However, such comparisons between risk factors can be misleading. It is not appropriate to treat only one of the major risk factors for microvascular complications of diabetes while ignoring or only partially treating other risk factors. Similar conclusions also can be applied to the prevention of macrovascular complications. Based on the data of the UKPDS, reduction of BP alone does not eliminate the excess rate of diabetic complications. Indeed, increasing

degrees of hyperglycemia have progressively greater rates of complications in the UKPDS for any given degree of BP control.

KEY POINT

Hypertension is perhaps more important than hyperglycemia as a risk factor for developing complications of diabetes, especially microvascular complications such as retinopathy and nephropathy.

As with the management of all other chronic illnesses, the management of hypertension requires the establishment of clear and well-defined treatment goals. The Joint National Commission on the Treatment of Hypertension (JNC) has issued 6 different sets of guidelines for the control of hypertension in adults in America. The most recent guidelines, JNC-VI, advocate a treatment target of 130/85 mm Hg, which includes patients with diabetes. However, these guidelines do suggest that lower pressures may be appropriate in patients with diabetes in view of comorbid conditions or complications.

Subsequent to the JNC-VI guidelines, a number of interventional trials have appeared that have suggested lower BP targets may be more appropriate in diabetic patients. The UKPDS embedded a 1200-patient hypertension control trial within the larger overall glycemetic control study. Patients were randomized to intensive versus less intensive BP control. Intensive management targeted a diastolic BP of 80 mm Hg. The patients with intensive management were further subdivided into initial therapy with an angiotensin-converting enzyme (ACE) inhibitor (captopril) or with a β -blocker (atenolol). At the end of the trial, the attained diastolic pressure averaged 82 mm Hg in the intensive management group compared with an attained diastolic pressure of 87 mm Hg in the less intensive management group. This difference of 5 mm Hg produced a 37% decline in microvascular

end-stage complications of diabetes and a similar decline in macrovascular events as well. The findings therefore suggest that a treatment target of 80 mm Hg may be more appropriate for patients with diabetes than the previously recommended 85 mm Hg.

Support for this concept is provided by the Hypertension Optimal Treatment (HOT) Trial (24), a multicenter, multinational trial involving ~19,000 patients throughout Europe. Of the participants ~8% had diabetes at the time of entry. Three different diastolic treatment targets were defined: 90, 85, and 80 mm Hg. Outcomes with respect to macrovascular complications were analyzed. In nondiabetic patients, no significant differences between the groups could be detected; however, in the diabetic subpopulation, a clear and significant difference was noted at each diastolic pressure treatment target. The group targeting a diastolic pressure of 85 mm Hg had one-third fewer major CV events than the group targeting 90 mm Hg. The group targeting 80 mm Hg had a two-thirds reduction in major CV events compared with the group targeting a diastolic of 90 mm Hg. These differences were highly statistically significant. Further, CV mortality was reduced two thirds in the group randomized to a diastolic goal of 80 mm Hg, compared with those randomized to a diastolic goal of 90 mm Hg. It seems reasonable to conclude then that based on randomized, controlled interventional trials a BP target of <130/80 is a desirable treatment target for patients with diabetes and should be adhered to in the absence of any clinical criteria that mitigate against this degree of BP control.

A vigorous debate has arisen over the choice of initial antihypertensive agents in diabetes patients. To some extent, this discussion of pharmacodynamic properties of one class of antihypertensive agents versus another and the potential benefits to be realized in diabetes patients becomes moot when considering the average patient with type 2 diabetes and hypertension generally requires 3 or more antihypertensive agents to attain the desired systolic and diastolic pressure goals. Thus, less effort on choosing the best first agent for BP management seems desirable and more effort on treatment titrations with multiple agents seems appropriate.

Over the years, numerous studies have suggested unique and clearly beneficial properties of ACE inhibition with respect to the prevention or the delay of progression of diabetic nephropathy. These studies have clearly demonstrated that ACE inhibition with agents such as captopril and enalapril not only reduces the degree of microalbuminuria or macroalbuminuria but also delays the deterioration in glomerular filtration rates and the time to dialysis in patients with overt nephropathy.

More recently, similar studies have been performed with angiotensin receptor blocker (ARB) compounds. These agents have the additional advantage of relatively diminished cough, the latter being a common complication of the use of ACE inhibitors. A provocative study, the Heart Outcomes Prevention Evaluation (HOPE) Trial (25), suggested that with essentially identical degrees of BP control, the inclusion of an ACE inhibitor (ramapril) may produce additional CV risk reduction as compared with placebo. In this study ramapril was also associated with a reduced risk of type 2 diabetes in an otherwise high-risk but previously nondiabetic population. It seems reasonable to conclude from these and many other trials that the use of an ACE inhibitor or an ARB, or both, seems appropriate initial therapy for the management of hypertension in patients with diabetes. They may also be useful for the treatment and possibly the prevention of the chronic microvascular and macrovascular complications of diabetes, and may therefore be considered even in normotensive patients with diabetes.

Certainly, normotensive patients who have rapidly rising BP from a previously low level to a higher, but yet normal level, should be considered for ACE inhibition or ARB therapy. Long-term observations suggest that such patients will be at considerably increased risk for the complications of diabetes and that these BP changes, while yet within the normal range, will ultimately culminate in the appearance of clinical hypertension in the majority of these patients.

The choice of second-line therapy for the management of hypertension in diabetic patients is more controversial. Clear and convincing clinical trial data are readily available regarding the bene-

fits of β -adrenergic inhibition using selective or nonselective β -blockers. In the UKPDS, no difference could be discerned between patients randomized to atenolol or to captopril as initial therapy in patients with diabetes.

Many other studies meanwhile have demonstrated significant benefits in both diabetic and nondiabetic patients with regard to recurring CV events and reduction of sudden death in patients receiving β -adrenergic inhibition. Thiazide diuretics are also associated with clear treatment benefits and improved outcomes in diabetic patients, particularly among the elderly. Furthermore, diuretics are particularly useful in the management of salt-sensitive hypertension—a common problem in the management of hypertension in African American patients. In the latter group, ACE inhibition may sometimes be less efficacious than in other ethnic groups, but the addition of a diuretic frequently overcomes this treatment deficiency. Because of the high prevalence of ischemic coronary disease and the 6- to 9-fold greater incidence of heart failure in diabetic compared with nondiabetic patients, the use of β -adrenergic blockade is preferred as second-line therapy in most patients. In African American patients diuretic therapy may be a better choice as second-line therapy. Certainly if either the first- or second-line therapies fail to achieve adequate BP control, then all 3 agents should be used in combination.

Other agents, such as calcium channel blockers, peripheral vasodilators, and centrally acting agents may be used as necessary. All of these, however, appear to have somewhat less desirable characteristics with respect to diabetes and are generally more controversial and are not favored over ACE or ARB therapy, β -adrenergic inhibition, or diuretic therapy. Regardless of which agent is considered, it should be prescribed with a view toward individual patient characteristics. For example, a patient with diabetic autonomic neuropathy and orthostasis is a poor candidate for a peripheral vasodilator; but a patient with diabetic diarrhea should receive a trial of clonidine therapy. Frequent monitoring of patients and medical adjustments may be necessary to maintain goals once they are attained.

DOES THE CHOICE OF THERAPY MODIFY THE RISK OF CV COMPLICATIONS?

Over the years, numerous clinical trials have attempted to define whether glycemic control improves CV complications of diabetes and whether there are unique advantages or disadvantages to the various antidiabetic therapies. Early trials, such as the University Group Diabetes Program (UGDP), perceived an excess CV risk associated with first-generation sulfonylurea therapy and with phenformin* compared with insulin therapy. Questions arose, however, regarding the trial design and randomization in several trial sites. The conclusions, certainly with respect to sulfonylureas, are open to question. Excess mortality from phenformin no doubt occurs as the result of excess lactic acidosis from this particular biguanide, possibly resulting from rates of phenformin clearance with variable blood levels as the consequence. Phenformin was withdrawn from the US market in 1977 and from most markets outside the United States as well. Based on this study, numerous authorities advocated insulin as the primary therapy for diabetes patients. In subsequent years, however, a number of studies have implicated insulin as potentially atherogenic. These have included a variety of epidemiologic analyses of populations as well as experimental studies using in vitro techniques.

Although there is little doubt that insulin is a growth-promoting hormone that may influence the proliferation of vascular smooth muscle cells, an important component of atherogenesis, no evidence has appeared to link insulin administration to excess atherosclerosis. This is true in the insulin-resistant patients with type 2 diabetes who were given insulin in the UKPDS and in type 1 diabetic patients in the DCCT with intensive compared with conventional insulin therapy. Better control with larger amounts of insulin, or with insulin compared to diet, was associated with a trend toward a reduction in the absolute rate of CV events. However, in both the UKPDS and the DCCT, these reductions did not attain statistical significance. It is possible to see in a variety of epidemiologic trials that

insulin-resistant subjects—particularly with high circulating insulin levels—have excess CV risk. Patients already insulin resistant with type 2 diabetes who are administered still more insulin may have no further increase in risk even if insulin is itself atherogenic in these insulin-sensitive individuals. However, the latter point is not at all clear and may not be a valid concern regarding insulin administration in either type 1 or type 2 diabetic patients.

Concerns have also arisen regarding second-generation sulfonylureas, such as glyburide, and ischemic preconditioning, a necessary adaptive response to short-term ischemia in the coronary circulation. While the UGDP clearly found excess CV morbidity and mortality with sulfonylureas, the UKPDS found no such excess. It did demonstrate a small but not statistically significant treatment benefit of sulfonylureas compared with diet and exercise alone. Glyburide was one of the sulfonylureas in the UKPDS, and this particular agent has been suggested as having fairly potent effects in antagonizing ischemic preconditioning. However, it has been observed that diabetic patients lack ischemic preconditioning. Furthermore, the concentrations of glyburide necessary to impair ischemic preconditioning, owing to its binding to the potassium channel in the coronary circulation of cardiac muscle, are considerably beyond the concentrations normally associated with glyburide therapy. Thus, these concerns may ultimately be groundless in the patient population under treatment, and certainly no convincing demonstration of excess mortality has yet to come forward with regard to glyburide or other second-generation sulfonylureas.

Notwithstanding these concerns, it seems clear that better agents may exist for the management of diabetes, at least as initial therapies. There can be little doubt from the results of the overweight cohort of the UKPDS that subjects randomized to initial treatment with metformin showed a clearly defined and statistically significant treatment benefit of metformin, compared with other therapeutic options for reducing atherosclerotic complications of diabetes. Complications such as myocardial infarctions and CV mortality were reduced in the cohort randomized to metformin

* Not FDA approved.

compared with those randomized to diet and exercise. Overweight patients randomized to sulfonylureas or insulin showed a reduction in CV events that was half or less than that seen with metformin, and these did not attain statistical significance. These treatment benefits of metformin were not explainable by differential benefits in glycemic control, body weight, lipid profiles, or BP.

Investigators in the UKPDS were unable to adequately assign the treatment benefit of metformin to any measured parameter in this study; however, it is useful to remember that metformin has clear insulin sensitizing properties. Furthermore, since insulin resistance is a state of accelerated atherogenesis, improvements in insulin sensitivity and its metabolic derangements resulting from metformin therapy may well be the likely mechanism by which improved CV outcomes were produced in this patient population. Regardless of the precise mechanism for this benefit—and in light of the lack of weight gain with metformin compared with other treatments for type 2 diabetes—it seems reasonable to conclude that metformin should be the preferred first-line antidiabetic therapy compared with sulfonylureas primarily because of its apparent treatment benefit to the CV complications of diabetes.

In more recent years, another class of more powerful insulin-sensitizing agents known as the thiazolidinediones have appeared. Unlike metformin, these agents enhance insulin action by activating a nuclear orphan receptor class, the peroxisome proliferator-activated receptor- γ , and appear to be more powerful at improving insulin sensitivity and in reversing the metabolic disturbances associated with insulin resistance. Thus, the nonglycemic effects of these agents, ranging from improvements in endothelial dysfunction to reduction of vascular inflammation, a key component of arterial atherogenesis, may be quite useful. Rosiglitazone therapy, for example, has been shown to improve or normalize the abnormal LDL particle size distribution and to substantially raise HDL cholesterol levels in type 2 diabetes. A number of randomized, prospective multicenter trials are under way to test the hypothesis that thiazolidinedione therapy may be associated with the

reduction of CV endpoints in diabetes patients. Until trial results are available, it seems reasonable to conclude, based on various in vivo and in vitro experimentation, that thiazolidinediones appear to have a reasonably good antiatherogenic potential and should therefore be included early in the course of diabetes management.

CONCLUSIONS

It seems clear that much of the excess CV risk of diabetes is not directly glucose derived. Scrupulous attention toward the identification and treatment of both traditional and the newer nontraditional CV risk factors will greatly reduce ischemic coronary events in diabetic patients. Furthermore it seems clear that a substantial reduction, if not normalization, of the excess CV risk is possible given the diagnostic techniques and pharmacologic agents presently available and the willingness to use them to the treatment standards now advocated based on recent clinical research.

REFERENCES

1. Nathan DM. Commentary. Some answers, more controversy, from UKPDS. *Lancet*. 1998;352:832–833. 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.
2. Jarrett RJ, McCartney P, Keen H. The Bedford survey: Ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia*. 1982;22:79–84.
3. Grundy SM. The National Cholesterol Education Program (NCEP)—The National Cholesterol Guidelines in 2001, Adult Treatment Panel (ATP) III. Approach to lipoprotein management in 2001 National Cholesterol Guidelines. *Am J Cardiol*. 2002;90:11i–21i.
4. Krolewski AS, Warram JH, Valsania P, et al. Evolving natural history of coronary artery disease in diabetes mellitus. *Am J Med*. 1991;90:56S–61S.
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444.
6. Colwell JA. The feasibility of intensive insulin management in non-insulin-dependent diabetes mellitus. Implications of the Veterans Affairs Co-

- operative Study on Glycemic Control and Complications in NIDDM. *Ann Intern Med.* 1996;124 (1 Pt 2):131–135.
7. 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.
 8. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI). *Circulation.* 1997;96:1761–1769.
 9. Islam MA, Blankenship JC, Balog C, et al, for the EPISTENT Investigators. Effect of abciximab on angiographic complications during percutaneous coronary stenting in the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial (EPISTENT). *Am J Cardiol.* 2002;90:916–921.
 10. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994;308:81–106.
 11. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation.* 1990;82:495–506.
 12. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care.* 1997; 20:614–620.
 13. Goldberg RB, Mellies MJ, Sacks FM, et al, for the CARE Investigators. 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. *Circulation.* 1998;98:2513–2519.
 14. 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.
 15. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomised placebo-controlled trial. *Lancet.* 2002;360:7–22.
 16. Hunninghake DB. Is aggressive cholesterol control justified? Review of the Post-Coronary Artery Bypass Graft Trial. *Am J Cardiol.* 1998;82: 45T–48T.
 17. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol.* 2002;40:2125–2134.
 18. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317: 1237–1245.
 19. Rubins HB, Robins SJ, Collins D, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med.* 1999;341: 410–418.
 20. Committee of Principal Investigators for the WHO Clofibrate Trial. WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: Mortality follow-up. *Lancet.* 1980;2:379–385.
 21. Haim M, Benderly M, Brunner D, et al. Elevated serum triglyceride levels and long-term mortality in patients with coronary heart disease: The Bezafibrate Infarction Prevention (BIP) Registry. *Circulation.* 1999;100:475–482.
 22. Steiner G. The Diabetes Atherosclerosis Intervention Study (DAIS): A study conducted in cooperation with the World Health Organization. The DAIS Project Group. *Diabetologia.* 1996;39: 1655–1661.
 23. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. *BMJ.* 1998;317:703–713.
 24. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet.* 1998;351:1755–1762.
 25. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000;355: 253–259.

Dialogue Box

EDITORIAL BOARD

Do statins afford a cardioprotective benefit independent of their lipid-lowering effect?

GARBER

It's been argued for years whether there's a pleiotropic effect of statins that extends beyond lipid lowering. Although still an area of controversy, it's clear from the Heart Protection Study that by using a statin you seem to get a similar proportional reduction in CV mortality regardless of the patient's LDL level. If there is evidence of ongoing atherosclerosis, LDL in a diabetic patient, no matter what the measured level, is suboptimal and the patient would benefit from further LDL reduction by the addition of a statin. Whether statins actually exert an independent non-LDL benefit remains an area of speculation.

EDITORIAL BOARD

What is your approach to the diabetic patient taking a statin agent whose LDL-cholesterol has reached goal but whose HDL-cholesterol continues to be low?

GARBER

I use a 3-step approach. First, I encourage lifestyle changes that raise HDL levels—this usually means increased physical activity and exercise. Second, I work harder to optimize control of the patient's diabetes and check to see whether the patient's drug regimen includes agents that have beneficial effects on HDL, eg, thiazolidinediones have a more favorable impact on HDL levels than do sulfonylurea agents. Third, if the patient has a sufficiently low HDL (<40 in a male and <50 in a female) and particularly if there is hypertriglyceridemia, I treat the dyslipidemia by starting a nicotinic acid or fibric acid agent.

EDITORIAL BOARD

The VA HIT would seem to support a role for gemfibrozil in such a patient. Why do you favor niacin?

GARBER

For a couple reasons. First of all, although fibric acid derivatives are effective agents for lowering triglycerides, they're not effective at raising HDL. Second, their use can be problematic if the patient is already taking a statin since there's evidence that gemfibrozil can inhibit the glucuronidation and clearance of many statins. Thus, you run the risk of doubling or tripling statin blood levels and increasing the risk for statin toxicity and the development of myopathy. Although the metabolic issue does not appear to be a concern with other fibrates, it should not be overlooked that published studies using fenofibrate or bezafibrate have failed to demonstrate the CV benefit provided by gemfibrozil as demonstrated in the VA HIT.

EDITORIAL BOARD

Please comment on the myopathy associated with statin use and reports that it can exist in the presence of normal muscle enzyme levels (ie, creatine kinase).

GARBER

Statin-associated myopathy is a significant problem and should be considered even if the patient's creatine kinase levels are normal. For patients taking statins who complain of significant muscle pain, regardless of their creatine kinase levels, my strategy is to reduce the statin down to the lowest dose tolerated and then add ezetimibe. With ezetimibe, you get an 18% reduction of LDL in addition to whatever the low-dose statin agent provides. For many patients, the reduction achieved

Dialogue Box

by adding ezetimibe to a low-dose statin is comparable to that attained with the higher, symptom-provoking statin dose.

EDITORIAL BOARD

In a patient taking 40 mg/d of atorvastatin with an LDL below 100 mg/dL, a serum triglyceride of 300 mg/dL, and an HDL of 35 mg/dL, do you add a niacin agent or a fibrate?

GARBER

In such a patient, it is much easier to add an agent such as Niaspan[®] rather than a fibrate. If you add gemfibrozil to a patient already taking 40 mg/d of atorvastatin, the risk of myopathy becomes a matter of concern.

EDITORIAL BOARD

What is your approach to a patient with hypertriglyceridemia and a low HDL who wants to drink more alcohol after learning of alcohol's beneficial impact on HDL?

GARBER

After informing the patient that alcohol will aggravate hypertriglyceridemia and is a significant source of calories, I would tell that patient that he or she owes me 2 miles on the treadmill for each alcoholic drink.

EDITORIAL BOARD

Is there still a reluctance to use nicotinic acid in the diabetic patient because of concerns of it hindering glycemic control?

GARBER

Not really, since for most patients its use requires only a minor adjustment of their diabetic medications. In fact, in a recent paper by Grundy (3), it was found that the adverse glycemic effect of

niacin was relatively small, on the order of 3/10th of an HbA_{1c} percent even at a high dose.

EDITORIAL BOARD

Some diabetic patients who are normotensive based on daytime readings exhibit hypertensive readings at night. What is your therapeutic approach to such a patient?

GARBER

One approach is to manipulate the drug regimen to where the patient takes a higher dose of blood pressure medication at night. Another option is to prescribe an α -blocker at bedtime since these agents appear to be particularly effective overnight. On a pathophysiologic basis, it has been observed that diabetic patients who tend to become hypertensive during the night are generally those who tend to be volume expanded. In such patients, giving them diuretics early in the evening before they go to bed can remedy the problem.

EDITORIAL BOARD

Do you routinely start a diabetic patient on an ACE inhibitor or an ARB once microalbuminuria develops even if the blood pressure is normal?

GARBER

Absolutely, and I titrate the dose upward with the goal of making the microalbuminuria disappear.

EDITORIAL BOARD

If the microalbuminuria persists despite maximum doses of an ACE inhibitor, do you attempt to further reduce glomerular pressure by adding a second drug?

Dialogue Box

GARBER

Yes. I add either an ARB or a calcium channel blocker (CCB), specifically a nondihydropyridine agent such as diltiazem.

EDITORIAL BOARD

Are you just as aggressive in the patient with macroalbuminuria?

GARBER

Yes, I am. I try to slow down the loss of protein in the urine as much as possible using an ACE inhibitor followed by the addition of a CCB or ARB as needed. Recognize, though, that once the patient develops macroalbuminuria, the renal decline becomes irreversibly progressive. The rate of decline may be reduced with good treatment but, it's still going to be progressive.

EDITORIAL BOARD

In the HOPE trial, ramipril was associated with a reduced risk of type 2 diabetes. Any thoughts as to how this potential benefit might be explained?

GARBER

It's possible that ramipril overcomes endothelial dysfunction, an important aspect of insulin resistance. By reversing insulin resistance, type 2 diabetes might possibly be prevented since this would effectively result in an unloading of beta cells in the pancreas.

EDITORIAL BOARD

What do you tell your patients taking statin agents regarding grapefruit juice?

GARBER

I advise them not to drink it. Narangin, which is

the active ingredient in grapefruit juice, is a cytochrome p450 3A4 blocker and thus any drug, including the statins, that goes through 3A4 may pose a problem. This is even more likely to be an issue with a longer-acting statin like Lipitor®.

EDITORIAL BOARD

In the interest of preventing CV disease, do you routinely strive for tighter diabetic control than a glycated hemoglobin below 7%?

GARBER

Yes. Recognize that a glycated hemoglobin of 6.5% represented the first point of elevated risk in the UKPDS. In light of this, current guidelines of the American College of Endocrinology, which were published in the January 2002 issue of *Endocrine Practice*, call for treatment goals of fasting glucoses of 110 mg/dL and a glycated hemoglobin of 6.5%.

EDITORIAL BOARD

Would you prescribe an insulin sensitizing agent in patients meeting NCEP criteria for the metabolic syndrome even in the absence of impaired glucose tolerance?

GARBER

Absolutely. In fact, metformin is the standard treatment now as far as I can tell for polycystic ovarian syndrome, particularly if reproduction is the goal. By reducing hyperandrogenemia and insulin resistance, metformin is beneficial since it reduces the consequences of androgen excess.

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