Cardiovascular disease is the most prevalent and detrimental complication of diabetes mellitus. The incidence of cardiovascular mortality in diabetic subjects without a clinical history of previous cardiac events is as high as the incidence in non-diabetic subjects with a history of myocardial infarction. This inordinate increase in the risk of coronary events in diabetic patients is attributed to multiple factors, including glycation and oxidation of proteins and increased prevalence of classic risk factors of coronary disease, such as hypertension, obesity, and dyslipidemia. Despite advances in the management of cardiovascular disease, a large proportion of diabetic subjects continue to have uncontrolled hyperglycemia, hypertension, and dyslipidemia. In addition, certain medical interventions with established efficacy in the general population do not appear to be appropriate for diabetic subjects. Recently published clinical trials of managing coronary risk factors indicate that more stringent goals of therapy should be set for diabetic patients. In this communication, some of these landmark studies are reviewed and some practical guidelines of management are suggested.

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Cardiovascular Disease in Type 2 Diabetes Mellitus

Current Management Guidelines

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Cardiovascular Disease (CVD) is the most prevalent complication of diabetes mellitus. It is estimated that 77% of hospitalizations in the United States for chronic complications of diabetes are attributable to CVD.1 The outcome of these hospitalizations is more often than not detrimental. The age-adjusted cardiovascular mortality is at least 2-fold higher in diabetic men than in nondiabetic subjects in the presence of any number of major risk factors.2 The survival after myocardial infarction is worse in diabetic men and women.3 The incidence of death from cardiovascular causes in diabetic subjects without a history of myocardial infarction during a 7-year follow-up was similar to the incidence observed in nondiabetic subjects with a history of myocardial infarction.4 These observations highlight the high prevalence of undiagnosed CVD in diabetics and the gravity of cardiovascular events in this population. The problem of undiagnosed disease is in part the result of lack of awareness by the patients of the strong association between diabetes and CVD. A recent survey commissioned by the American Diabetes Association and the American College of Cardiology found that almost 70% of people with diabetes do not realize that they are at increased risk of CVD and stroke (http://www.theheart.org HeartWire > News; February 20, 2002; accessed March 2002).

One of the most disconcerting observations is that, although the CVD mortality in nondiabetic men and women was reduced by 36.4% and 27.0%, respectively, during a decade of follow-up, the CVD mortality in diabetic men was reduced by only 13.1% and in diabetic women was actually increased by 23.0% during the same period of observation.5 The changes in diabetic subjects did not reach statistical significance. This suggests that certain interventions that have been useful in reducing the CVD mortality in the general population have been either less efficacious or sometimes detri-
mental in diabetic patients. An example of the latter is the finding that, for diabetic patients with multivessel disease, coronary artery bypass grafting is superior to percutaneous coronary angioplasty, while in nondiabetic subjects, the outcome of the 2 procedures is similar. It remains to be conclusively shown whether the advent of arterial stents and potent antiplatelet therapy will be equally beneficial in diabetic and nondiabetic subjects.\(^\text{10}\)

Multiple factors contribute to the accelerated atherosclerosis in diabetes. These factors include excess prevalence of traditional risks such as obesity, hypertension, and dyslipidemia along with modifications of lipoproteins and other key proteins with glycation and oxidation, increased procoagulation, and possibly the state of insulin resistance. In this communication, the data from key clinical trials will be reviewed and some of the management guidelines developed in consensus conferences will be summarized.

**LIFESTYLE MODIFICATIONS**

Obesity is a common problem in diabetes and is estimated to account for approximately 60% of type 2 diabetes. The central distribution of fat and history of weight gain in addition to body mass are independent risks of developing diabetes. A recent statement from the American Heart Association acknowledges the importance of targeting obesity to prevent cardiovascular disease.\(^\text{24}\) Therefore, obesity is a rational target for the management of type 2 diabetes. The current dietary recommendations emphasize restriction of saturated fat to less than 7% of daily caloric intake and restriction of cholesterol to less than 200 mg/dL. In addition, the use of dietary stanols and fish oil supplements may be considered in some patients. Although the optimal dietary composition is not well established, the benefits of modest caloric restriction are well recognized. Recent clinical interventions with modest caloric restriction and increased physical activity have shown that the onset of diabetes can be significantly delayed and possibly prevented with modest weight loss.\(^\text{31,32}\) In the same study, the use of metformin was associated with 31.8% reduction in risk of type 2 diabetes.\(^\text{21}\) If lifestyle modifications are not sufficient to achieve at least 5% to 15% weight loss, then pharmacologic and possibly surgical interventions should be considered. The 2 antiobesity agents approved by the Food and Drug Administration in the United States, namely sibutramine hydrochloride and orlistat, have been used in patients with type 2 diabetes and have been found to be associated with amelioration of cardiovascular risk factors in this population.\(^\text{33-36}\)

The precise cause of increased cardiovascular morbidity and mortality in obesity is not known. Observational studies suggest that it may be related to insulin resistance and hyperinsulinemia.\(^\text{37}\) However, hyperinsulinemia induced by either exogenous insulin administration or the use of insulin secretagogues such as sulfonylureas does not appear to promote atherosclerosis.\(^\text{38}\) Future interventional trials using insulin sensitizers may uncover a possible pathogenetic role of insulin resistance in susceptible individuals.

**MANAGEMENT OF HYPERGLYCEMIA**

Although the value of tight glycemic control in the prevention of microvascular disease in type 1 and 2 diabetes is undisputable, its role in preventing macrovascular disease has been debated.\(^\text{38,45-51}\) Two elegant studies, one in patients admitted with myocardial infarction and the other in critically ill patients after cardiac surgery, have clearly shown that intensive insulin therapy with the goal of normalizing blood glucose levels reduces hospitalization days and saves lives. The largest interventional trial in patients with type 2 diabetes showed that, although the reduction of glycosylated hemoglobin (HbA\(_1c\)) from a mean of 7.9% to a mean of 7.0% was associated with 16% reduction in myocardial infarction, the change did not achieve statistical significance (\(P = .052\)).\(^\text{38}\) However, analysis of all the data points available in this trial showed a significant correlation between HbA\(_1c\) achieved and the risk of cardiovascular deaths.\(^\text{54}\) A more recent epidemiologic study found a continuous relationship between all-cause mortality and HbA\(_1c\) even for values in the nondiabetic range.\(^\text{55}\) Thus, 16% risk reduction for a modest change in HbA\(_1c\) found in the United Kingdom Prospective Diabetes Study may well be biologically significant. Despite these uncertainties in the overall outcome of the study, in the subgroup of overweight patients randomized to the metformin arm of the study, there was 39% reduction in myocardial infarction, 42% reduction in diabetes-related deaths, and 36% reduction in all-cause mortality.\(^\text{56}\) These changes were statistically significant. The apparent increase in death related to diabetes in the subgroup of patients randomized to metformin-sulfonylurea combination was attributed to an unusually low mortality rate in the sulfonylurea arm of the study and short duration of follow-up, and because it could not be corroborated by the data from the overall population, the observation was considered to be a statistical fluke.

A role for postprandial hyperglycemia as an independent risk factor for CVD is now emerging.\(^\text{50,57}\) However, there are no universally accepted guidelines on how to target postprandial hyperglycemia. The American College of Endocrinology and the American Association of Clinical Endocrinologists Diabetes Mellitus Consensus Conference recommends a 2-hour postprandial glucose level of less than 140 mg/dL (7.8 mmol/L).\(^\text{58}\) On the basis of our clinical experience, we had earlier recommended a 1-hour postprandial glucose value of less than 160 mg/dL (8.9 mmol/L) as the target for achieving postprandial con-
control and adjustment of medications. Since HbA1c is the gold standard for measurements of diabetes control, the principal goal of therapy should strive to achieve HbA1c levels as low as possible without increasing the hypoglycemia risk or compromising the patient’s quality of life. Currently, the HbA1c goal recommended by the American Diabetes Association is less than 7.0%, while the American College of Endocrinologists and the European Diabetes Policy Group recommend an HbA1c goal of less than 6.5%.

These observations taken together indicate that tight glycemic control, especially in the critically ill and high-risk patients, would decrease mortality. The initial choice of therapy depends on multiple factors, notably the clinical state of the patient, the degree of hyperglycemia, coexisting medical problems, and the cost of the medications. In overweight individuals, initiation of therapy with metformin or metformin-containing combination therapy is advisable unless there is a specific contraindication to metformin use. A suggested algorithm of drug therapy is shown in Figure 1. The response to drug therapy should be monitored with home blood glucose monitoring, and medications should be adjusted to keep the fasting as well as postprandial blood glucose values within the individualized targets. The main impediments to achieving glycemic targets include inaccessibility to medical care, difficulties in adherence to prescribed regimens, fear of hypoglycemia, and inappropriate weight gain associated with some forms of therapy in a select group of patients. With the advent of a host of newer agents with diverse mechanisms of action, it will be feasible to achieve optimal blood glucose control in a larger number of subjects.

**MANAGEMENT OF DYSLIPIDEMIA IN DIABETIC SUBJECTS**

Stratification of risk factors for coronary heart disease (CHD) in type 2 diabetes shows that low-density lipoprotein (LDL-C) and high-density lipoprotein cholesterol (HDL-C) are the best predictors of CHD. However, the prevalence of high LDL-C level in diabetic subjects is not different from the prevalence rate in the non-diabetic population. In contrast, the prevalence of hypertriglyceridemia and low HDL-C levels in diabetic subjects is approximately twice as high as in the non-diabetic groups. Thus, management should target all lipid abnormalities identified in diabetic subjects. Although at the present time there are no major clinical outcome trials in exclusively diabetic patients, many currently available trials have enrolled a subgroup of subjects with diabetes. These trials indicate that cholesterol reduction with a statin is valuable in CHD risk reduction as both primary and secondary prevention. Of note is the recent demonstration that even those with normal or low cholesterol levels (ie, total cholesterol level <200 mg/dL [<5.2 mmol/L] or LDL-C level <120 mg/dL [<3.1 mmol/L]) will benefit from statin therapy. Because of the wealth of clinical experience with this class of agents, statins are the mainstay of therapy in diabetic dyslipidemia. However, recent clinical trials with different fibrates have shown a therapeutic role of this class of agents in the prevention of CHD.

The choice of a particular agent depends on the baseline lipid profile achieved after 6 to 12 weeks of intense lifestyle changes and possible use of dietary supplements such as stanols. A simplified algorithm of drug therapy for dyslipidemia in diabetic subjects is shown in Figure 2. The values of the serum lipid profile are not intended to represent goals of therapy, but rather are suggested as trigger points for initiation or modification of drug choices. If the predominant lipid abnormality is hypertriglyceridemia with serum triglyceride concentration greater than 500 mg/dL (5.6 mmol/L), then fibrates would be considered the first choice of therapy. In subsequent follow-up, when LDL-C level is greater than 130 mg/dL (3.4 mmol/L), then a statin is added as a combination therapy. Other options to be used in combination with the fibrate could include niacin, bile

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**Figure 1.** A suggested algorithm for the initiation of drug therapy to control hyperglycemia in diabetes mellitus (DM) (adapted with permission from Chehade and Mooradian; copyright 2001, John Wiley & Sons Limited). AGI indicates α-glucosidase inhibitors; FPG, fasting plasma glucose; PP, postprandial plasma glucose; SFU, sulfonylurea; and TZD, thiazolidinediones. To convert glucose levels to millimoles per liter, multiply by 0.0555.

**Figure 2.** A suggested algorithm of drug therapy for dyslipidemia in diabetes mellitus. LDL-C indicates low-density lipoprotein cholesterol; TG, serum triglyceride concentration. To convert TG to millimoles per liter, multiply by 0.0113; LDL-C, by 0.259.
acid–binding resin, or, when available, a cholesterol absorption inhibitor.72 On the other hand, if the serum triglyceride levels are less than 500 mg/dL (5.6 mmol/L) and the LDL-C values are greater than 130 mg/dL (3.4 mmol/L), then a statin would be the first drug of choice. The statin dose can be titrated up to achieve the therapeutic goal or, alternatively, a bile acid–binding resin is added if the serum triglyceride concentrations do not exceed 200 mg/dL (2.3 mmol/L). Otherwise, a fibrate, niacin, or, when available, a cholesterol absorption inhibitor would be considered. The use of a drug combination as first-line therapy is also an alternative; however, the clinical experience with this approach is limited. The combination of a statin with a fibrate or niacin increases the risk of rhabdomyolysis, and therefore a low dose of statins (10-20 mg) or a statin with the least drug interaction potential, such as pravastatin sodium, should be used.

The use of niacin to treat dyslipidemia in patients with type 2 diabetes has been discouraged because of the potential increase in insulin resistance.94 It appears that if the dose of niacin is limited to less than 2 g/d, the effect on insulin resistance is modest.73 Nevertheless, in an occasional patient with impaired glucose tolerance, the initiation of niacin treatment may precipitate overt diabetes. In addition, a substantial number of patients (up to 30%) may not tolerate the adverse effects associated with niacin therapy.

Some of the newly available insulin sensitizers, such as pioglitazone hydrochloride, have significant favorable effects on serum triglyceride and HDL-C levels, and these effects are independent of their effects on blood glucose control.74 Therefore, such agents may also be considered as adjunct therapy for diabetic dyslipidemia.

The goals of therapy were recently updated by the Adult Treatment Panel III of the National Cholesterol Education Program.26 This panel considers diabetes as a CHD risk equivalent and sets the LDL-C goal at less than 100 mg/dL (2.6 mmol/L). In addition, desirable serum triglyceride levels should be less than 150 mg/dL (1.7 mmol/L) and HDL-C, greater than 40 mg/dL (1.0 mmol/L). The Adult Treatment Panel III identifies non–HDL-C (ie, total cholesterol minus HDL-C) as a secondary target of therapy in patients with serum triglyceride levels equal to or greater than 200 mg/dL (2.3 mmol/L). In subjects with diabetes, the non–HDL-C goal is 130 mg/dL (3.4 mmol/L).26 Unfortunately, a substantial number of patients fail to achieve these goals.75 The task of achieving the lipid therapy goals in a larger number of patients will be greatly facilitated with the advent of more powerful agents that can be used safely in combination with other agents with distinct mechanisms of actions.

**BLOOD PRESSURE CONTROL**

Hypertension awareness, treatment, and control are improving in the United States. However, of those with hypertension, 31.6% are still unaware that they have high blood pressure, only 27.4% are receiving antihypertensive medications and are under control, 26.2% are on medications but remain uncontrolled, and 14.8% are not taking any antihypertensive therapy at all.70 Overall, less than one third of hypertensive patients who are being treated for hypertension have their blood pressure under control despite the overwhelming evidence in favor of controlling hypertension.76 This is especially true for high-risk patients such as those with diabetes.

The results from United Kingdom Prospective Diabetes Study indicate that the risk of myocardial infarction and microvascular end points correlate with the blood pressure in patients with type 2 diabetes.77 In that study, the mean blood pressure achieved in the intensively treated subjects was 144/82 mm Hg, and in the conventional arm of the study, 154/87 mm Hg. Despite this modest difference in blood pressure, the risk of diabetes-related death was reduced by 32%; that of stroke, by 44%; and that of congestive heart failure, by 56%.77 The study also found that captopril and atenolol were equally safe and effective.77 However, this conclusion is debatable given that the design of the study was not optimal to detect drug-specific outcomes.

In the Systolic Hypertension in the Elderly Program, the effect of systolic blood pressure control with chlorthalidone with and without atenolol or reserpine on cardiovascular events was studied over 5 years. A 34% risk reduction was observed in diabetic patients (n=583). This was similar in magnitude to the risk reduction seen in the nondiabetic group (n=4149).78 The effect of systolic blood pressure control with ni- trendipine was also studied in the Systolic Hypertension in Europe Trial.79 The diabetic group (n=492) had 70% risk reduction, while the nondiabetic group (n=4203) had 16% risk reduction.79 Primary prevention in diabetic patients was also observed in the study of ramipril on cardiovascular events.80 Finally, the Hypertension Optimal Treatment trial found that, in diabetic patients, targeting diastolic blood pressure to be less than 80 mm Hg is associated with greater risk reduction than the risk reduction observed in those who achieve diastolic blood pressure of less than 90 or 85 mm Hg.81

According to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the goal of blood pressure control should be 130/85 mm Hg.79 The goal of blood pressure control according to the American Diabetes Association is 130/80 mm Hg.60 Similarly, the National Kidney Foundation recommends a more stringent goal of 130/80 mm Hg, and, if proteinuria of more than 1 g/d is documented, then the goal is 125/75 mm Hg.82

The choice of the therapeutic agent depends on multiple variables. In general, angiotensin-converting enzyme inhibitors or angiotensin II blockers are recommended as first-line therapy if nephropathy is present.60,85-87 The Heart Outcomes Prevention Evaluation study suggests that angiotensin-converting enzyme inhibitors may have the additional benefit of CVD and diabetes prevention.80,88 In those with established CVD, β-blockers are recommended unless the patient has hypoglycemia unawareness (ie, is unable to detect the early warning signs
of hypoglycemia). Of note, some studies have found that the dihydropyridines are less effective in preventing the progression of renal disease, and, as such, they should be used only if other alternatives are not tolerated or ineffective. A recent study found that irbesartan was more effective than amlodipine in reducing the progression of diabetic nephropathy when given with other drugs to control blood pressure. It is also noteworthy that the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggested that α-blockers may have less benefit in this population than diuretics and β-blockers. In the latter study, the α-blocker arm of the study was stopped by the data and safety monitoring committee because of increased incidence of heart failure. However, α-blockers may be useful in a subgroup of patients with symptoms of benign prostatic hypertrophy and in those in whom other antihypertensive agents are ineffective.

A subgroup of diabetic subjects who pose a therapeutic dilemma include those with supine hypertension and orthostatic hypotension. These patients may benefit from a trial of clonidine patch and judicious use of short-acting α-adrenergic agonists such as midodrine hydrochloride. An alternative approach is bedtime use of short-acting agents such as oral clonidine or captopril. The availability of a wide variety of antihypertensive agents allows the physician to prescribe an agent with maximal efficacy and limited side effect profile. It is now possible to achieve the goals of blood pressure control in a large number of patients without compromising the quality of their lives.

THE ROLE OF ANTIOXIDANTS

Oxidative stress has been implicated in atherosclerosis. Since diabetes is considered a state of increased oxidative load, and some patients may have occasional micronutrient deficiencies, it is tempting to speculate that supplementation with antioxidants may prevent CVD in diabetes. However, the relationship of antioxidants to atherosclerosis is moot. Whereas epidemiologic studies suggest a favorable role of dietary and possibly supplemental intake of antioxidants, interventional trials by and large have failed to show beneficial results, and some studies have suggested that antioxidant supplementation may have deleterious effects on health. One randomized study found that vitamin E supplementation at 400 mg/d but not at 800 mg/d is associated with reduced incidence of nonfatal myocardial infarctions. The overall mortality was not changed. However, a more recent trial of simvastatin with and without a cocktail of antioxidants including vitamins E and A and ascorbic acid found that use of antioxidants was associated with reduced efficacy of simvastatin in increasing HDL levels. Ongoing interventional trials may shed some additional light on this controversy. Meanwhile, it is prudent not to consume vitamins or minerals in excess of their recommended dietary intake limits.

THE ROLE OF ANTIPLATELET THERAPY

Type 2 diabetes is a state of increased plasma coagulability. The platelet aggregability is increased and fibrinolytic capacity is reduced. Antiplatelet therapy, notably use of aspirin, has been shown to be effective in reducing CVD-related events. The recommended dose and frequency of administration is somewhat controversial. In most patients, 325 mg/d is recommended. If excessive bruising occurs, then a dose of 81 mg/d is advisable. Clopidogrel bisulfate, another antiplatelet agent with a different mechanism of action, is also an alternative. In one large trial, clopidogrel appeared to be more potent than aspirin in reducing cardiovascular events. In addition, in a recent trial in patients with acute myocardial infarction, clopidogrel therapy was associated with a significant reduction in event rate compared with aspirin alone. Thus, in diabetic patients who experience a cardiovascular event while taking aspirin therapy, clopidogrel therapy should be considered. The recent demonstration that a substantial number of people may have a relative resistance to antiplatelet effects of aspirin is of concern. Future studies are needed to address this confounding variable and to determine whether individualizing aspirin dose would enhance its cardioprotective properties.

NOVEL RISK FACTORS

It is generally accepted that only approximately 50% of myocardial infarctions can be attributed to the classic lipid risk factors. A host of lipid and non–lipid-related risk factors have been studied. Of these risk factors, microalbuminuria is a major predictor of cardiovascular events. It is likely that the microalbuminuria is a marker of generalized endothelial dysfunction in diabetes. The beneficial role of angiotensin-converting enzyme inhibitors and angiotensin II blockers in patients with microalbuminuria is well established. Although there is no conclusive evidence, a case can be made for using these agents prophylactically to prevent the emergence of proteinuria in diabetic subjects.

The C-reactive protein level has emerged as another valuable independent predictor of cardiovascular disease both in men and in women. In addition, statin therapy is associated with reduced C-reactive protein levels independent of its effect on serum lipid levels. Diabetic subjects tend to have higher C-reactive protein levels than nondiabetic control subjects, suggesting that an ongoing inflammatory response may be contributing to the accelerated atherosclerosis in diabetes.

Another emerging risk factor is lipoprotein(a). Many studies have shown a correlation between lipoprotein(a) and coronary heart disease. The recent Atherosclerosis Risk in Communities Study reported that lipoprotein(a) added only modest predictive value to LDL-C, HDL-C, and total triglycerides.

Finally, plasma homocysteine levels have been found to be associated with CVD in diabetic and non-diabetic subjects. However, this association was modest compared with the predictive role of C-reactive protein. It remains to be seen whether lowering plasma homocysteine levels with folic acid...
or cyanocobalamin supplementation would reduce risk of coronary heart disease.137

CONCLUSIONS

The prevalence of diabetes is increasing worldwide.138 The number of people with cardiovascular morbidity will also increase. Some of the mechanical interventions that have been helpful in the general population have not been found to be useful in diabetic subjects. In addition, the risk of sudden death in diabetic patients without known heart disease is as high as the rate seen in nondiabetic subjects with a history of myocardial infarction. Thus, it is imperative that the efforts at treating this disease emphasize preventive approaches. Early screening and identification of risk factors, including testing for microalbuminuria, should be instituted. Earlier and more rigorous control of blood pressure may well be the most important therapeutic strategy. The goals of therapy have to be individualized, taking into account the patient's coexisting medical problems and ability to adhere to prescribed regimens. Although screening for an underlying subclinical CVD is recommended for high-risk diabetic subjects planning to embark on a moderate- to high-intensity exercise program, in most patients the physician should use clinical judgment in recommending exercise or pharmacologic stress tests.139 Overall, it appears that diabetic subjects would benefit from a more aggressive preventive program that sets more stringent standards. It is likely that achieving these goals is a challenging task. Nevertheless, these measures are bound to reduce the incidence of cardiovascular morbidity and mortality in a very high-risk group of people.

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