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Prevention, diagnosis, and treatment of cardiovascular disease in patients with diabetes

The poor outcomes associated with diabetic coronary artery disease can be prevented or improved with pharmacological therapies including ASA, beta-blockers, ACEI, and statins as well as lifestyle changes that include smoking cessation and increased physical activity.

ABSTRACT: Most adult patients with diabetes are at high risk for cardiovascular disease, the primary cause of morbidity and mortality in this population. Multifactorial intervention aimed at reducing major risk factors may decrease cardiovascular events by up to 50%. Pharmacological approaches targeting hypertension and dyslipidemia are extremely effective. Nonpharmacological approaches to diabetes prevention and cardiovascular risk reduction are also very effective. Screening for cardiovascular disease followed by appropriate intervention can help prevent the poor outcomes associated with diabetic coronary artery disease. Patients with diabetes who are either symptomatic or have abnormal screening test results should be started immediately on ASA, beta-blockers, ACE inhibitors and, where indicated, statins or other lipid-lowering agents. At the same time, these patients should be referred to a specialist for further invasive testing.

There is now solid evidence that proper pharmacological and nonpharmacological management of the major risk factors for cardiovascular disease (CVD) has a significant beneficial impact on morbidity and mortality in patients with type 2 diabetes (DM2).[1-2] While the United Kingdom Prospective Diabetes Study (UKPDS) suggested that controlling glycemia may not have a significant impact on macrovascular disease (although P=.052 is "marginally significant"),[3] one arm of the study demonstrated significant decreases in morbidity and mortality when patients with diabetes were treated for hypertension.[4] The Diabetes Atherosclerosis Intervention Study of lowering lipid levels with fenofibrate showed an improvement in several parameters of coronary angiography, although the number of participants was too small to demonstrate an overall benefit in cardiovascular events.[5] The large Heart Protection Study[6] as well as the subgroup analysis of the Scandinavian Simvastatin Survival Study reported beneficial effects of simvastatin on cardiovascular mortality in patients with diabetes.[7] There is now a general consensus that lowering lipid levels decreases cardiovascular morbidity and mortality in patients with diabetes, and most national and international guidelines recommend aggressive treatment of lipids.

Pharmacological approaches to risk reduction

A recent study has shown that multifactorial intervention has the greatest impact on preventing CVD in patients with DM2.[1] In this study, 80 patients were randomly assigned to receive conventional therapy (in accordance with their national guidelines) and 80 patients received intensive therapy with a vigorous implementation of behavior modification and pharmaco-

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logical therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria. All patients received ASA. The targets for the intensive therapy group were glycosylated hemoglobin <5%, BP <130/80 mmHg, total cholesterol levels <4.5 mmol/L, and triglycerides <1.7 mmol/L. In addition, the patients in the intensive therapy group received lifestyle intervention aimed at a reduced intake of dietary fat, increased participation in exercise, and cessation of smoking. These patients were also taking ASA, vitamin C, folic acid, and chromium picolinate (a dietary supplement). To slow the progression of renal disease, an ACE inhibitor or, where indicated, an angiotensin receptor blocker was added, regardless of blood pressure. The patients in the conventional therapy group received ACE inhibitors after the year 2000. The trial was conducted, on average, over 7.8 years. The cardiovascular events comprised death from cardiovascular causes, nonfatal myocardial infarction or stroke, coronary or peripheral artery revascularization, or amputation of limbs as a result of ischemia. One or more events occurred in 44% of patients in the conventional therapy group, but only in 24% of patients in the intensive therapy group. In addition, rates of nephropathy and neuropathy were also markedly reduced in the intensive therapy group.

While the design of this study did not allow researchers to identify which intervention was the most effective, the results indicate that aggressive lifestyle and pharmacological therapy is effective in reducing cardiovascular death. Questions have been raised as to the feasibility of routine use of ACE inhibitors and the role of glucose management in the observed reduction of vascular events.[2] Prevailing opinion still holds that tight control of glycemia may not be decisive for prevention of the macrovascular complications, and that control of blood pressure and lipids plays a greater role. The other questions concern lifestyle measures and dietary supplements. While the subjects in this study were on a low total and low saturated fat diet, recent data suggest that replacing saturated fats, and particularly trans-fatty acids, with monounsaturated fats may be more beneficial. There is currently no evidence that either vitamins E or C, or any other antioxidants affect cardiac outcomes.

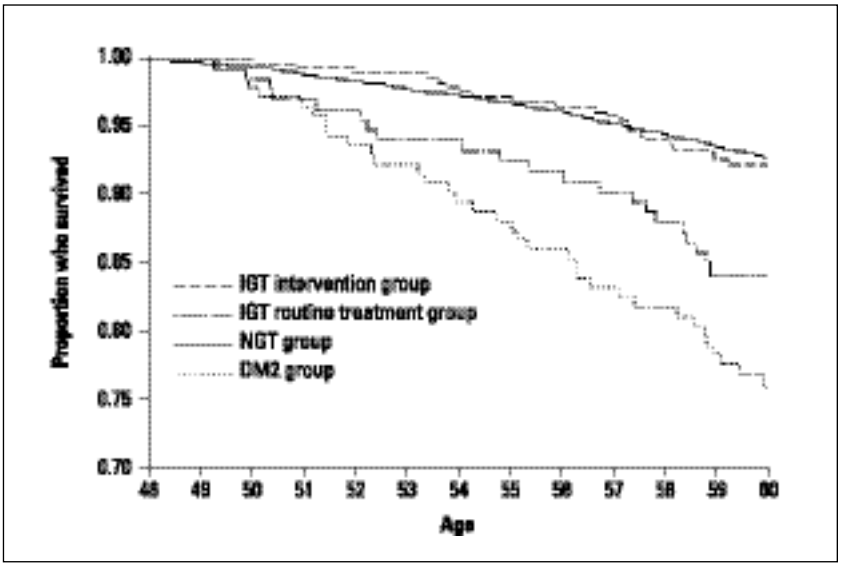

Figure 1. Survival curves (Kaplan-Meyer life-table analysis) of the four study groups in the Malmo Preventive Trial.[12]

Mortality in the IGT intervention group did not differ from that in the NGT group (P=.80), but was lower than that in the IGT routine treatment group (P=.009) and that in the DM2 group (P=.0001) (log-rank test). Figure used with permission from Springer-Verlag.

Nonpharmacological approaches to risk reduction

Substantial evidence suggests that smoking cessation and a physically active lifestyle are related to a reduction in the risk of CVD and DM2. When physically active patients are compared with sedentary patients, the risk reductions for the active patients are estimated to be 35% to 55% for CVD and 30% to 50% for DM.[8-10] In addition, regular exercise has been shown to have a beneficial impact on glycemic control.[11]

Two recent trials have demonstrated that lifestyle changes, including increased physical activity, are associated with decreased mortality in patients with DM2 and patients with impaired glucose tolerance (IGT). In a 12-year follow-up (see **Figure 1**) of a large group of Swedish men (~7000), those who developed IGT had a mortality rate two times higher than those with normal glucose tolerance (NGT). Importantly, those in the IGT intervention group who participated in a program of increased physical activity and dietary counseling had all-cause mortality rates 50% lower than those in the IGT routine treatment group (without lifestyle intervention). The IGT routine treatment group and the DM2 group had similar rates of excess mortality compared with those in the NGT group.[12]

Similar results were seen in a study of 1263 men with DM2 over an average 12-year follow-up. After adjustment for the traditional cardiovascular risk factors, the least fit of this group had a two times higher risk of all-cause mortality than the most fit of the cohort. A separate measure of self-reported physical activity similarly demonstrated that lower levels of physical activity were associated with a risk of mortality 1.7 times higher.[13] Thus, low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality in men with DM2, and promotion of physical activity is vital in the prevention and management of DM2.

Diagnosis and treatment of cardiovascular disease in DM2 patients

Patients with diabetes often have blunted anginal symptoms secondary to cardiovascular autonomic neuropathy. This makes screening for CVD in otherwise asymptomatic patients (most often initially with an exercise tolerance test or ETT) of particular importance. The American College of Cardiology (ACC) along with the American Diabetes Association (ADA) have developed guidelines for screening DM2 patients (see **Table 1**).[14] Screening using the ACC/ADA guidelines will establish a diagnosis of significant CVD in 5% to 15% of asymptomatic diabetic patients. Surprisingly, only 30% to 50% of diabetic patients with symptoms compatible with CVD have a positive stress test.[15] For this reason, the appropriate timing of treatment and referral is critical.

All asymptomatic diabetic patients should be sent for a baseline electrocardiogram (ECG). If this is normal and the patient does not meet any of the criteria in **Table 1**, no further testing or treatment is required and the patient should be followed on an annual basis. If resting ECG abnormalities suggest ischemia or infarction, or the patient fulfills any of the criteria in **Table 1**, further testing is required. Normally, risk stratification is done with the standard ETT in asymptomatic diabetic patients. As with the ACC and American Heart Association guidelines for nondiabetic patients, those unable to ambulate or those who have baseline ECG abnormalities should proceed directly to cardiac radionuclide imaging. In the meantime, ASA therapy should be initiated.[16] If ASA is contraindicated because of previous gastrointestinal bleeding or documented allergy, then clopidogrel is a reasonable alternative, although it should be noted that this indication was not specifically addressed in a recent clopidogrel trial.[17]

If an asymptomatic diabetic patient has an abnormal ETT result or radionuclide scan, the patient should be immediately started on the agents discussed below, while invasive testing and referral to an internist or cardiologist is being arranged. In addition to ASA or clopidogrel, a beta-blocker should be started, as this class of drugs confers significant morbidity and mortality benefits in patients with diabetes.[18] It should be noted that the risk of hypoglycemia is not increased in patients with diabetes who are taking cardioselective beta-blockers.[19] As described in the Heart Outcomes Prevention Evaluation Study, ACE inhibitors also confer a substantial mortality benefit in this population and should be started immediately.[20] Use of statins has also been associated with a decrease in CVD morbidity and mortality in a number of studies.[6,7,21]

Patients with diabetes who have symptoms of ischemic heart disease on initial presentation should immediately start on the above medications prior to any testing. A timely referral to an internist or cardiologist is indicated, as these patients will likely require early invasive testing.

Table 1. Indications for cardiac testing in diabetic patients.

1. Typical or atypical cardiac symptoms.
2. Resting ECG abnormalities suggestive of ischemia or infarction.
3. Peripheral or carotid occlusive disease.
4. Sedentary lifestyle, age >35 years, and plans to begin an exercise program.
5. Two or more of the following risk factors:
   - Total cholesterol >6.0 mmol/L, LDL-C >4.0 mmol/L, HDL-C <0.9 mmol/L
   - BP >140/90 mm Hg
   - Smoking
   - Family history of premature coronary artery disease
   - Positive microalbuminuria/macroalbuminuria test

Source: American College of Cardiology and American Diabetes Association.

Acute coronary syndrome

Glycoprotein IIb/IIIa inhibitors, beta-blockers, and ACE inhibitors are all equally efficacious in both diabetic and nondiabetic patients with an acute coronary syndrome. The only additional management concern is the evidence from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction Study that showed a mortality benefit at 30 days and 1 year with strict glycemic control in the postinfarct period.[22]

With regard to thrombolytic agents, both the Thrombolysis and Angioplas-

ty in Myocardial Infarction (TAMI) trial and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial demonstrated similar infarct-related patency rates in diabetic and nondiabetic subgroups.[23,24] There was no increased risk of intraocular hemorrhage from diabetic retinopathy in these trials.

Goals of therapy

For adult patients with diabetes, Canadian guidelines call for LDL cholesterol <2.5 mmol/L and a total: HDL cholesterol ratio of <4.0, or apolipoprotein B <0.9 g/L. Measurement of apolipoprotein B is the best single follow-up test, as it is a better predictor of outcome than LDL cholesterol. Current Canadian consensus guidelines on hypertension recommend a target BP <130/80 mm Hg for patients with diabetes, and a target BP <125/75 mm Hg for patients with diabetes who have proteinuria >1 g/24 h.[25] Although the initial recommended agent would be an ACE inhibitor or an angiotensin receptor blocker, more than two-thirds of patients in the most recent hypertension trials have required multiple medications to reach BP targets.

Revascularization

Patients with diabetes tend to have more diffuse coronary artery disease and higher restenosis rates after percutaneous coronary intervention. For this reason, patients with diabetes have a higher referral rate for coronary artery bypass graft (CABG) surgery than nondiabetics. The Bypass Angioplasty Revascularization Trial randomized patients with multivessel disease to CABG or percutaneous transluminal coronary angioplasty (PTCA).[26] At 5 years, patients with treated diabetes who went for CABG had a higher survival rate than those who went for PTCA (8% vs 66%).

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Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is currently enrolling patients to test whether a strategy of early revascularization reduces morbidity and mortality in patients with type 2 diabetes whose cardiac symptoms are mild and stable.[27] It will also assess whether treatment to attenuate insulin resistance can arrest or retard progression of coronary artery disease more effectively than an insulin-providing approach.

Summary

Adult patients with diabetes are at high risk for cardiovascular disease—similar to the risk of nondiabetic patients who have already sustained a myocardial infarction—and thus must have their modifiable risk factors treated aggressively. Appropriate screening and treatment can improve outcomes associated with diabetic coronary artery disease. It is critical that symptomatic patients and asymptomatic individuals with abnormal screening test results immediately start therapy with ASA, beta-blockers, ACE inhibitors and, where indicated, statins or other lipid-lowering agents. These measures should be started at the same time as arrangements are made for referral to a specialist for further invasive testing.

Competing interests

Dr Frohlich has acted as a consultant or speaker for most pharmaceutical companies that produce lipid-lowering medications, and has obtained unrestricted research grants from several of these companies, including AstraZeneca, Merck Frosst, and Pfizer.

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