Complications of diabetes

A four-article symposium

Symposium coordinator: Nancy J. V. Bohannon, MD
Physician in private practice of endocrinology

VOL 105 / NO 2 / FEBRUARY 1999 / POSTGRADUATE MEDICINE

Management of diabetes has improved greatly in the past few decades, but the disease and its complications continue to exact an enormous toll on society. In the United States, diabetes is the seventh leading cause of mortality, the sixth leading cause of death by disease, and the leading cause of new blindness. Its economic impact is enormous. Our nation spends about $92 billion annually on diabetes--$45 billion directly for healthcare and $47 billion indirectly for disability, work loss, and early death. As grim as these statistics are, we can still point to the impressive progress that has been made in understanding and limiting the impact of this disease.

Control is, of course, the key to effective management of diabetes, but new information is helping us rein in complications and prevent additional problems if complications do occur. For example, cardiovascular disease risks in patients with diabetes are well known but often underappreciated. In fact, diabetes is the most common cause of myocardial infarction in persons under age 30 in the United States. Secondary prevention thus becomes especially important, particularly since appropriate intervention can drastically alter the long-term picture for many patients. The first article in this symposium reviews a number of studies that validate the use of lipid-lowering therapy in diabetic patients with coronary artery disease. Angiotensin-converting enzyme inhibitors, beta blockers, and antiplatelet agents also play an important part in secondary prevention.

The second article discusses management of diabetic nephropathy and highlights ways it can be prevented or controlled. Drs Bell and Alele point out that the natural history of renal disease suggests that function declines at a rate of about 10% per year once macroalbuminuria develops. However, several treatment regimens can slow this decline and prolong the active life of the kidney. In particular, exacting and aggressive control of hypertension and glucose levels can delay and even prevent onset of diabetic nephropathy.

In the third article, Drs Aljahlan, Lee, and Toth describe cheiroarthropathy, or limited joint mobility, in patients with diabetes mellitus. Although this painless disorder usually affects only the small joints of the hands and is seldom a significant problem in itself, it can be an important clue to more serious microvascular complications of diabetes.

Traveling with diabetes presents challenges because of time changes, unpredictable meal schedules, and variations in exercise and sleep routines. In the final article in this symposium, Drs Dewey and Riley discuss prevention and management of diabetic emergencies when traveling.

Diabetes is a far more complex disease than was recognized at the time many of us went to medical school. New information emerges monthly, and staying on top of changes is challenging. We hope this symposium helps you understand some of the new thinking.

Coronary artery disease and diabetes

Secondary prevention needs more attention

Nancy J. V. Bohannon, MD

VOL 105 / NO 2 / FEBRUARY 1999 / POSTGRADUATE MEDICINE

This is the first of four articles on complications of diabetes

Preview: Although diabetes clearly increases the risk for cardiovascular disease, secondary prevention often is overlooked in diabetic patients. Clinical trials show that aggressive lipid-lowering therapy provides significant benefit in diabetic patients with coronary artery disease, often to an even greater extent than in the nondiabetic population. In this article, Dr Bohannan looks at a number of secondary prevention strategies for patients with diabetes and discusses when and why to use them.

The high prevalence of large-vessel coronary artery disease (CAD) in diabetic patients is well recognized, but the magnitude of this problem is not always appreciated. Data from the 18-year Framingham Study (1) show that the relative risk for CAD in diabetic men and women 45 to 74 years of age is 2.4 and 5.1 times greater, respectively, than for age-matched nondiabetic men and women. In the Islington Diabetes Survey (2), the prevalence of serious CAD increased from 9% in subjects with normal glucose tolerance to 17% in those with impaired glucose tolerance and 20% in those with diabetes.

Diabetes is the most common cause of myocardial infarction (MI) in persons under age 30 in the United States. One study (3) over a 3 1/2-year period showed an increase in CAD events in a subset of subjects who had the highest hemoglobin A1c (HbA1c) levels. CAD-related mortality in both men and women with type 1 (formerly called insulin-dependent) or type 2 (formerly known as non-insulin-dependent) diabetes mellitus is much greater than in nondiabetic populations (4). Like CAD events, CAD mortality also increases with increasing HbA1c levels (3).

In addition, diabetes has an adverse impact on survival after MI. At 70 months after MI, survival is about 50% for men and 40% for women with diabetes, compared with 70% for men and 75% for women without diabetes (5).

Cardiovascular diseases other than CAD are also more prevalent in diabetic patients than in the nondiabetic population. Diabetes increases the risks of cerebrovascular disease, peripheral vascular disease, and congestive heart failure (6-8). Estrogen does not seem to protect premenopausal diabetic women from premature cardiovascular disease, as it does in women who do not have diabetes. Even at a young age, women with diabetes have almost the same risk for cardiovascular disease as men with diabetes and a much greater risk than men without diabetes.

Coronary risk factors

The impact of diabetes on CAD mortality is equivalent to that of a combination of any two of the other traditional risk factors, such as

hypertension and smoking. In other words, the age-adjusted cardiovascular mortality rate is as great in a person in whom diabetes is the only cardiovascular risk factor than in a person without diabetes but with two other classic risk factors. Furthermore, the presence of diabetes greatly increases the risk of cardiovascular disease associated with any other risk factor.

Multiple cardiovascular risk factors are more common in diabetic than in nondiabetic persons. Hypertension develops in about 50% of diabetic patients. About half of the type 2 diabetes patients have dyslipidemia, and about 80% are obese.

Insulin resistance or endogenous hyperinsulinemia (a marker for insulin resistance) is thought to increase cardiovascular risk and may contribute to the higher prevalence of CAD in the type 2 diabetes population (9,10). Endogenous hyperinsulinemia has been linked to CAD (11,12), even after adjustment for age, body mass index, smoking habits, alcohol use, systolic blood pressure, medications, family history of ischemic heart disease, and levels of triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and apoprotein B (table 1). Although this adverse impact may be due to the hyperinsulinemia itself, recent evidence suggests that it is not (13).

Table 1. Effect of diabetes on lipid levels

	Total cholesterol	LDL cholesterol	HDL cholesterol	VLDL cholesterol	Triglycerides
Type 1, well controlled	Average*	Average	Average	Average	Average
Type 1, poorly controlled	Increased	Average or increased	Decreased	Increased	Increased
Type 2, well controlled	Average to increased	Plus or minus average	Decreased	Plus or minus average	Greatly increased
Type 2, poorly controlled	Increased	Increased	Decreased	Greatly increased	Greatly increased

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.
*Average means usual levels for the nondiabetic American population.

According to a 1996 Consensus Statement of the American Diabetes Association (ADA) (14), the hyperinsulinemia associated with non-insulin-dependent diabetes mellitus, hypertension, dyslipidemia, obesity, and atherosclerotic cardiovascular disease (Reaven's syndrome or metabolic syndrome X) is likely to be a marker of the insulin-resistant state rather than a causative agent in the specific components of the syndrome.

Hyperinsulinemia may contribute to atherosclerosis through stimulation of smooth-muscle cell migration and proliferation, matrix deposition, inhibition of fibrinolysis, up-regulation of LDL cholesterol binding, down-regulation of HDL cholesterol binding, or increases in arterial wall lipid synthesis or deposition (10,15). Furthermore, elevated hepatic insulin levels may affect formation by the liver of procoagulants (ie, factor X, von Willebrand factor, fibrinogen) that may play an important part in cardiovascular disease.

Type 2 diabetes is associated with a procoagulant state with increased levels of many coagulation factors, including fibrinogen, von Willebrand factor, and thrombin activity; increased platelet aggregability and thromboxane release; and decreased fibrinolytic activity due to elevated levels of plasminogen activator inhibitor, type 1 (PAI1) (7,8,15). However, hyperinsulinemia may merely be a marker for insulin resistance, which could itself modulate metabolic processes leading to the increased risk (10,11).

Levels of lipoprotein(a) and PAI1 (which is thought to be an independent risk factor for recurrent MI) are often elevated in diabetic patients. PAI1 influences the atherothrombotic process by decreasing fibrinolytic activity, thereby predisposing to thrombus formation due to fibrin deposition. Lipid-lowering drugs, such as lovastatin (Mevacor), have been found to decrease PAI1 levels by 20% to 30%.(16)Interestingly, the antidiabetic insulin-sensitizing medication metformin hydrochloride (Glucophage) has also been found to decrease PAI1 by 20% to 25% (17).

Diabetic nephropathy and microalbuminuria may also influence atherogenicity. Microalbuminuria, even in the absence of diabetes, has been found to increase the risk of CAD. Both diabetic nephropathy and microalbuminuria can be adversely affected by lipid levels and by angiotensin-converting enzyme (ACE) activity (18). A statistically significant correlation between the rate of decline of the glomerular filtration rate (GFR) and elevated total cholesterol, triglyceride, and apolipoprotein-B levels was detected in a 2(1)/2-year follow-up of 30 patients with type 1 diabetes and advanced nephropathy (19).

Increases in monocyte adhesion to the endothelium, impaired endothelial cell adhesion to the extracellular matrix, and impaired spreading may contribute to the endothelial dysfunction that often accompanies vascular disease in diabetic patients.

Dyslipidemia and diabetes

Hypertriglyceridemia is the most common lipid abnormality in diabetic patients and is a known risk factor for CAD when associated with diabetes, hypertension, and hyperapolipoproteinemia B. It also is associated with increased thrombosis and thrombotic potential. According to prospective data (20), hypertriglyceridemia also appears to be a major coronary risk factor in men with abnormal glucose tolerance.

Benefits of lipid-lowering therapy

The goals for secondary prevention in both diabetic and nondiabetic patients are stabilization of existing lesions to decrease their thrombogenicity, prevention of the formation of new lesions, and improvement of endothelial function. The 1998 ADA guidelines (21) recommend LDL cholesterol levels under 100 mg/dL, HDL cholesterol above 45 mg/dL, and triglyceride levels under 200 mg/dL for most diabetic patients.

Improvement of diabetic control, whether through sulfonylurea drugs, metformin, or continuous subcutaneous insulin infusion, leads to improvement in total cholesterol, LDL cholesterol, and total triglyceride levels (22). However, other forms of intervention may be needed to achieve optimal lipid management.

The Helsinki Heart Study (23), a primary prevention study, showed that gemfibrozil (Lopid) induced greater lipid changes in patients with type 2 diabetes than in nondiabetic subjects. A statistically significant reduction in the 5-year incidence of CAD deaths and MI was seen with gemfibrozil in nondiabetic subjects. An even greater reduction was evident in diabetic patients, although the change was not statistically significant because of the low number (135) of diabetic patients in the study.

Subset analysis of data from the Scandinavian Simvastatin Survival Study (24) and the Cholesterol and Recurrent Events (CARE) study (25) indicates that aggressive lipid-lowering therapy can significantly reduce the rate of clinical events in diabetic as well as nondiabetic patients. In fact, the benefits in diabetic patients treated with lipid-lowering drugs in these two secondary prevention studies were even greater than in the nondiabetic population.

In the simvastatin (Zocor) trial (24), 202 (4.5%) of the 4,444 participants were initially recognized as having diabetes. The lipid changes seen in the diabetic subgroup treated with simvastatin were similar to those observed for the simvastatin-treated group as a whole. However, the diabetic patients had a 56% reduction in risk of coronary events compared with the placebo-treated diabetic patients. The nondiabetic group showed a 32% reduction in risk. Despite the greater reduction in risk among patients with diabetes, the absolute risk for coronary events in simvastatin-treated diabetic patients remained greater than in nondiabetic subjects treated with the drug.

Simvastatin reduced the risk of total mortality by 43% in diabetic patients, compared with 29% in the nondiabetic population. However, despite treatment with simvastatin, absolute mortality was greater in patients with diabetes (14%) than in those without (8%). Mortality was also greater in diabetic patients treated with simvastatin (14%) than in nondiabetic subjects given placebo (11%). Mortality in the diabetic group treated with placebo was higher than in any other group.

Information from the simvastatin study was recently reevaluated (25) using the new ADA criteria for diagnosis of diabetes. When a fasting plasma glucose level of 126 mg/dL was used as a criterion, an additional 281 subjects were identified as having diabetes, for a total of 483 diabetic patients in the study. Recalculation showed the relative risk of major coronary events among diabetic patients treated with simvastatin (including the 281 relatively milder, undiagnosed cases) to be 0.58 (P=.001); the relative risk for revascularization was found to be 0.53 (P=.006).

When a fasting plasma glucose level of 110 to 125 mg/dL was used as the criterion for impaired fasting glucose, 678 subjects were identified. Relative risk for the group randomly assigned to simvastatin treatment was 0.44 for coronary mortality (P=.005), 0.60 for major coronary events (P=.001), 0.57 for revascularization (P=.010), and 0.54 for total mortality (P=.015). Thus, use of simvastatin in this impaired fasting glucose group resulted in a 46% reduction in total mortality, 56% reduction in coronary mortality, 40% reduction in major coronary events, and a 43% reduction in revascularization procedures, all of which were statistically significant.

The 502 diabetic patients enrolled in the CARE study (26) (a study in which total cholesterol average was normal and LDL cholesterol near normal at baseline, despite documented MI) represented 14% of the study population. Analysis of this subgroup indicated a significant reduction in coronary events in those treated with pravastatin sodium (Pravachol) compared with those given placebo. The nondiabetic pravastatin-treated population had a 22% reduction in coronary events at the end of the 5 1/2-year study, compared with a 27% reduction in the diabetic subgroup (P=.001). Both reductions were statistically significant, but the reduction in diabetic patients was of greater significance (26).

Other interventions

Proteinuria is associated with increased CAD risk in both diabetic and nondiabetic patients. Therapies that reduce proteinuria in diabetic patients or that

interfere with factors that promote or worsen proteinuria are also likely to decrease the risk of cardiovascular disease.

ACE inhibitor therapy decreases the rate of progression of diabetic nephropathy as well as the risk of cardiovascular disease. Likewise, use of lovastatin (18) to lower LDL levels in type 2 diabetic patients with type IV hyperlipoproteinemia decreases the rate of decline in the GFR.

Modification of insulin resistance through the use of metformin, an insulin sensitizer, decreases blood glucose levels by 20% to 30% and also reduces LDL cholesterol by up to 10% and triglycerides by 10% to 20% (27). Insulin levels, PAI1 activity, and fibrinogen, all of which have been found to be associated with increased cardiovascular risk, also decrease in response to metformin.

Another insulin sensitizer, troglitazone (Rezulin), decreases triglycerides by 10% to 30% but has no consistent effect on total or LDL cholesterol. PAI1 activity is reduced by 20% to 25% with lovastatin and pravastatin.

Several studies have demonstrated the value of aspirin therapy in both diabetic and nondiabetic persons. The Early Treatment Diabetic Retinopathy Study (28) showed a statistically significant reduction in the relative risk of MI in patients taking aspirin, compared with those not using aspirin. This study involved more than 5,000 diabetic patients, about one third of whom had type 1 and two thirds of whom had type 2 diabetes. MI occurred in 9.1% of the patients treated with aspirin, compared with 12.3% of those given placebo therapy (relative risk, 0.83).

In the Anti-Platelet Trialists' (APT) Collaboration (29), a meta-analysis of 140 antiplatelet trials, the incidence of total vascular events among diabetic patients was 18.5% in those treated with aspirin versus 22.3% in those receiving placebo (P=.002). The incidence of MI among the diabetic subjects in the Physicians' Health Study was 4% in the aspirin group, compared with 10.1% in the placebo group. This translated into a relative risk for MI of 0.39 in aspirin-treated diabetic patients.

Although complete inhibition of cyclooxygenase and thromboxane can be achieved with aspirin therapy in diabetic patients, platelet adhesion often remains elevated, possibly because of glycosylation of surface receptors. This leads to increased macrophage adhesion on the endothelium.

The 2 1/2-year follow-up trial of intravenous abciximab (ReoPro) (30), a monoclonal antibody fragment that blocks platelet aggregation, showed a statistically significant reduction in MI and the need for revascularization, compared with placebo therapy given to patients undergoing percutaneous coronary angioplasty. Although subset analysis has not yet been reported for the diabetic population, results of this analysis are eagerly anticipated. This approach to platelet inhibition may be an important intervention for reducing secondary CAD events in diabetic patients (31).

The Bezafibrate Infarction Prevention Study Group (32) examined the usefulness of beta-blocker therapy after MI in 2,723 diabetic patients. The 3-year total mortality was 7.8% in patients receiving beta blockers, compared with 14% in those who were not given beta blockers, a 44% reduction with beta-blocker therapy. A 42% reduction in cardiac mortality was also seen in patients who received beta blockers. The 3-year survival curves were significantly different and demonstrated increasing divergence (P=.0001). Multivariate analysis showed that beta-blocker therapy was a significant independent contributor to increased survival (relative risk, 0.58).

Recommendations for secondary prevention

Current recommendations for management of diabetic patients with CAD are similar to those for secondary prevention in nondiabetic patients. However, in the diabetic population intervention may be even more crucial, since diabetic patients are at relatively greater risk.

To date, studies analyzing secondary prevention have shown equal or greater benefit among diabetic patients compared with nondiabetic patients. Even concerns about potential confounding factors in this

population (ie, retinal bleeding with aspirin therapy, induction of unrecognized hypoglycemia, or interference with counterregulatory mechanisms with beta blockers) are overshadowed by the greater risk imposed by withholding secondary preventive therapy. The risk-benefit ratio has consistently fallen on the side of standard preventive post-MI therapy (ie, lipid-lowering therapy plus aspirin, beta blockers, and ACE inhibitors), provided there are no contraindications to the use of these drugs and diabetes is under good control.

The recent Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (33-35) evaluated mortality over a mean of 3.4 years in 620 diabetic patients. These patients were randomly assigned to receive either standard care or subcutaneous insulin-glucose infusion given as soon as possible after MI and continued for 24 hours in the hospital, followed by long-term subcutaneous insulin injection four times daily for at least 3 months. The insulin group had better diabetes control, with a decrease in blood glucose levels from 277 to 172 mg/dL during the first 24 hours, compared with a fall from 282 to 210 mg/dL in the standard-care group. There was a 0.9% decrease in HbA1c after 1 year in the insulin patients, compared with a 0.4% decrease in the standard-care group. Intensive control decreased relative risk of mortality by 29% after 1 year--from 26.1% in the standard-care group to 18.6% in the intensive-control group (P=.027).

An even more dramatic reduction in 1-year mortality was seen in a subset of patients with low cardiovascular risk, who had not previously been treated with insulin. In this group, in-hospital mortality was reduced by 58% (P<.05) and 1-year mortality by 52% (absolute mortality, 8.6% in the infusion group versus 18% in the standard-care group [P=.02]). The benefit of treatment within the first 24 hours and for at least 3 months persisted to the mean 3.4-year follow-up. The mortality rate for the treatment group was 33%, compared with 44% among the standard-care group (relative risk, 0.72 [P=.011]). These findings strongly suggest that intensive control of blood glucose, including insulin therapy, from the time of admission to the coronary care unit and continuing after discharge, should be used more often.

Recommendations for lipid modification

Since the coronary risk associated with diabetes is equal to that conferred by any other two CAD risk factors, it may be advisable to manage all diabetic patients with hypercholesterolemia as if they had high cholesterol levels plus two other risk factors. The recent recommendations from the ADA (21) stipulate a goal LDL cholesterol level of less than 100 mg/dL for all diabetic patients. If nondrug measures are insufficient to achieve this goal, drug therapy should be initiated if the LDL level is greater than 100 mg/dL and the patient has evidence of macrovascular disease or hypercholesterolemia plus two risk factors.

The hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are usually first-line therapy for lowering LDL cholesterol levels after MI in diabetic patients. Nondrug measures should, of course, be started at the same time, but drug intervention should not be postponed if the LDL cholesterol level is above 100 mg/dL. Therapy can be started in the hospital and continued after discharge unless specific contraindications exist.

In patients with type 2 diabetes (the majority of the diabetic population), nicotinic acid (niacin) is relatively contraindicated because it increases insulin resistance, contributes to hyperuricemia (to which many such patients are predisposed owing to the effect of insulin resistance or hyperinsulinemia on renal handling of uric acid), and could precipitate acute gout or dramatic worsening of diabetes control.

Bile acid-binding resins (ie, cholestyramine [Questran, Prevalite], colestipol hydrochloride [Colestid]) may lower LDL cholesterol levels but tend to raise triglyceride levels, which often are already high in patients with type 2 diabetes and may contribute to the procoagulant state. The resins also frequently cause constipation that can lead to patient-induced Valsalva maneuvers, which should be discouraged after MI. In addition, acute retinal hemorrhage and blindness can be precipitated by

the Valsalva maneuver in patients with proliferative diabetic retinopathy.

Gemfibrozil has been found to be particularly effective in preventing first coronary events in the subpopulation that has triglyceride levels above 200 mg/dL and total cholesterol-HDL ratios greater than 5, which describes the lipid profile of many patients with type 2 diabetes. However, these data are from a primary rather than a secondary prevention study, and the LDL cholesterol goal of less than 100 mg/dL established by the National Cholesterol Education Program for secondary prevention often cannot be reached with gemfibrozil therapy alone.

Other secondary prevention measures

Obesity should be addressed in the "window of opportunity" or "teachable moment" immediately after MI, since more than 80% of patients with type 2 diabetes are obese and obesity contributes to both insulin resistance and dyslipidemia. Consultation and ongoing follow-up with a dietitian are important adjunctive measures.

Now, more than ever, we can expect metabolically significant reductions in weight with drug treatment of obesity. This can result in improvements in lipid profile, blood pressure, insulin resistance, and hyperinsulinemia. Some of these drug therapies (eg, orlistat, tetrahydrolipstatin [Xenical]) should decrease hyperlipidemia even in the absence of significant weight loss.

Unless contraindicated, ACE inhibitors are first-line therapy for hypertension in diabetic patients because of their nephroprotective and cardioprotective effects. The goal blood pressure should be less than 130/85 mm Hg throughout the day. Low-dose beta blockers should be used for secondary prevention, if not contraindicated, even in the absence of hypertension, because of their ability to prevent recurrent coronary events. If hypertension is present, doses of beta blockers should be adjusted to control blood pressure as well.

Smoking cessation efforts should be intensified to achieve and maintain a nonsmoking status. Here, again, new pharmaceutical agents may be helpful.

A cardiac rehabilitation program should be prescribed and implemented to allow patients to safely resume exercise and increase aerobic capacity and cardiovascular fitness.

Antioxidant trials for secondary prevention of cardiovascular disease in diabetics are not yet completed, but many diabetologists and lipidologists routinely advise vitamin E (400 to 800 mg/day), vitamin C (500 to 1,000 mg/day), and folate (1 to 5 mg/day) to lower homocysteine levels.

Summary

The increased risk of cardiovascular disease in diabetic patients is well documented. A greater appreciation for the importance of this fact and regular use of secondary prevention strategies, including aggressive use of HMG-CoA reductase inhibitors or other lipid-lowering agents to reduce cholesterol levels, are clearly indicated for diabetic patients with CAD. If no contraindications exist, ACE inhibitors, beta blockers, and aspirin also should be considered for these high-risk patients.

References

1. **Kannel WB.** Lipids, diabetes, and coronary heart disease: insights from the Framingham study. Am Heart J 1985;110(5):1100-7
2. **Jackson CA, Yudkin JS, Forrest RD.** A comparison of the relationships of the glucose tolerance test and the glycated haemoglobin assay with diabetic vascular disease in the community: the Islington Diabetes Survey. Diabetes Res Clin Pract 1992;17(2):111-23
3. **Kuusisto J, Mykkanen L, Pyorala K, et al.** NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 1994;43(8):960-7
4. **Krolewski AS, Warram JH, Valsania P, et al.** Evolving natural history of coronary artery disease in diabetes mellitus. Am J Med 1991;90(2A):56S-61S
5. **Sprafka JM, Burke GL, Folsom AR, et al.** Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival: the Minnesota

Heart Survey. Diabetes Care 1991;14(7):537-43
6. **Gordon T, Castelli WP, Hjortland MC, et al.** Diabetes, blood lipids, and the role of obesity in coronary heart disease risk for women: the Framingham study. Ann Intern Med 1977;87(4):393-7
7. **Bierman EL.** George Lyman Duff Memorial Lecture: atherogenesis in diabetes. Arterioscler Thromb 1992;12(6):647-56
8. **Stamler J, Vaccaro O, Neaton JD, et al.** Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16(2):434-44
9. **Godsland IF, Stevenson JC.** Insulin resistance: syndrome or tendency? Lancet 1995;346(8967):100-3
10. **Katz RJ, Ratner RE, Cohen RM, et al.** Are insulin and proinsulin independent risk markers for premature coronary artery disease? Diabetes 1996;45(6):736-41
11. **Pyorala K, Savolainen E, Kaukola S, et al.** Plasma insulin as coronary heart disease risk factor: relationship to other risk factors and predictive value during 9(1)/2-year follow-up of the Helsinki Policemen Study population. Acta Med Scand Suppl 1985;701:38-52
12. **Fontbonne AM, Eschwege EM.** Insulin and cardiovascular disease: Paris Prospective Study. Diabetes Care 1991;14(6):461-9
13. **Stern MP.** Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? Ann Intern Med 1996;124(1 Pt 2):110-6
14. The pharmacological treatment of hyperglycemia in NIDDM. Diabetes Care 1996;19(S1):S54-61
15. **Pyorala K.** Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. Diabetes Care 1979;2(2):131-41
16. **Isaacsohn JL, Setaro JF, Nicholas C, et al.** Effects of lovastatin therapy on plasminogen activator inhibitor-1 antigen levels. Am J Cardiol 1994;74(7):735-7
17. **Grant PJ.** The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. Diabetes Care 1996;19(1):64-6
18. **Lam KS, Cheng IK, Janus ED, et al.** Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. Diabetologia 1995;38(5):604-9
19. **Mulec H, Johnsen SA, Wiklund O, et al.** Cholesterol: a renal risk factor in diabetic nephropathy? Am J Kidney Dis 1993;22(1):196-201
20. **Fontbonne A, Eschwege E, Cambien F, et al.** Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes: results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989;32(5):300-4
21. **American Diabetes Association.** Management of dyslipidemia in adults with diabetes. Diabetes Care 1998;21(1):179-82
22. **Dunn FL, Pietri A, Raskin P.** Plasma lipid and lipoprotein levels with continuous subcutaneous insulin infusion in type I diabetes mellitus. Ann Intern Med 1981;95(4):426-31
23. **Koskinen P, Manttari M, Manninen V, et al.** Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. Diabetes Care 1992;15(7):820-5
24. **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(4):614-20 [Erratum, Diabetes Care 1997;20(6):1048]
25. **Haffner SM, Alexander CM, Boccuzzi SJ, et al.** Improved survival, reduced major-coronary events and fewer revascularizations in simvastatin-treated 4S patients with impaired fasting glucose. Diabetes, Suppl 1, 1998;47:A54
26. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effect of pravastatin on coronary events

after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335(14):1001-9
27. **DeFronzo RA, Goodman AM.** Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus: the Multicenter Metformin Study Group. N Engl J Med 1995;333(9):541-9
28. **ETDRS Investigators.** Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. JAMA 1992;268(10):1292-300
29. **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(6921):81-106 [Erratum, BMJ 1994;308(6943):1540]
30. **Topol EJ, Ferguson JJ, Weisman HF, et al.** Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. JAMA 1997;278(6):479-84
31. **Kleiman NS, Lincoff AM, Kereiakes DJ, et al.** Diabetes mellitus, glucoprotein IIb/IIIa blockade, and heparin: evidence for a complex interaction in a multicenter trial: EPILOG investigators. Circulation 1998;97(19):1912-20
32. **Jonas M, Reicher-Reiss H, Boyko V, et al.** Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease: Bezafibrate Infarction Prevention (BIP) Study Group. Am J Cardiol 1996;77(15):1273-7
33. **Malmberg K, Ryden L, Efendic S, et al.** Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26(1):57-65
34. **Malmberg K, Ryden L, Hamsten A, et al.** Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes insulin-glucose in acute myocardial infarction. Eur Heart J 1996;17(9):1337-44
35. **Malmberg K.** Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ 1997;314(7093):1512-5