Vascular Medicine 2001; **6**: 249–255

Vascular complications in diabetes and their prevention

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Abstract: Diabetes mellitus is increasing throughout the world. Cardiovascular disease (CVD) accounts for up to 80% of excess mortality in this high-risk population. Patients with diabetes have the same CVD risk factors as those people without diabetes. However, these risk factors are much more powerful in diabetic patients. CVD risk is especially high for diabetic women, and premenopausal diabetic women lose all the protection normally afforded to them by female sex hormones. Controlled clinical trials have clearly demonstrated that rigorous treatment of blood pressure, dyslipidemia and platelet hyperaggrebility strikingly reduces CVD risk in diabetic patients. Strategies directed at interrupting the renin-angiotensin system (both tissue and systemic systems) and the use of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors have proven to be especially beneficial for this high-risk population.

Key words: atherosclerosis; diabetes; dyslipidemia; hypertension

Introduction

The incidence of diabetes, particularly type 2 diabetes, as well as the cost of its treatment and complications is increasing at a rapid rate in industrialized, westernized societies such as the USA.[1] The increasing prevalence of diabetes tracks with increases in aging, obesity, and sedentary lifestyles in these populations.[2] Type 2 diabetes is also more common in several minority populations, including Hispanics and African Americans, whose relative numbers are increasing in this country.[3] An estimated 15.7 million people in the USA are diabetic, of whom 5.4 million people are unaware of their disease. Diabetic patients tend to have more cardiovascular risk factors and worse clinical outcomes compared with patients without diabetes (Figure 1). Indeed, cardiovascular disease (CVD) accounts for up to 80% of the deaths in people with type 2 diabetes.[4] This review covers the various metabolic abnormalities in type 2 diabetes and their contributions to CVD, which is so prevalent and deadly in this population.

Macrovascular disease in diabetes

Many risk factors contribute to the high prevalence of macrovascular disease in people with diabetes. These factors include obesity, dyslipidemia, hyperinsulinemia, hyperglycemia, hypertension, coagulation abnormalities, platelets and endothelial dysfunction.

Obesity

Obesity is a powerful underlying factor that dramatically contributes to the increasing prevalence of diabetes in industrialized societies, particularly visceral obesity.

Visceral obesity, localized around omental and mesenteric tissues, is an especially strong risk factor for development of hypertension and diabetes. Visceral obesity is also associated with insulin resistance, hyperinsulinemia, and premature CVD.[5–12] The dyslipidemia associated with visceral obesity is characterized by low levels of high-density lipoprotein cholesterol (LDL-C), high triglyceride levels, and phenotypic small, dense, low-density lipoprotein (LDL) particles, which are more atherogenic, further contributing to accelerated atherosclerosis. The concentration of plasminogen activator inhibitor-1 (PAI-1) is also increased in association with visceral obesity, and this may in turn promote thrombosis.[12] Thus, visceral obesity may be the underlying common denominator for many of the metabolic risk factors associated with diabetes and hypertension (Table 1).

Hyperinsulinemia in cardiovascular diseases of diabetes

Increased lipid content within skeletal muscle seen in visceral adiposity contributes to insulin resistance and associated hyperinsulinemia.[6–8] Endogenous hyperinsulinemia may potentially promote atherosclerosis by a number of mechanisms. Insulin and insulin-like growth factor 1 (IGF-1) are structurally related, share receptors, and have a similar post receptor signaling pathway.[9] High levels of insulin stimulate mitogenic signaling pathways and increase DNA synthesis in vascular smooth muscle cells.[9] Insulin stimulates the synthesis of both endothelin and plasminogen activator inhibitor,[10] two atherogenic factors. The effect of insulin on cardiovascular growth and remodeling is likely mediated through actions on the IGF-1 receptor in vascular smooth muscle cells (VSMCs),[9] or mediated indirectly by stimulating VSMC or cardiac IGF-1 synthesis.[9–11] There is also increasing evidence that enhanced IGF-1 expression-syn-

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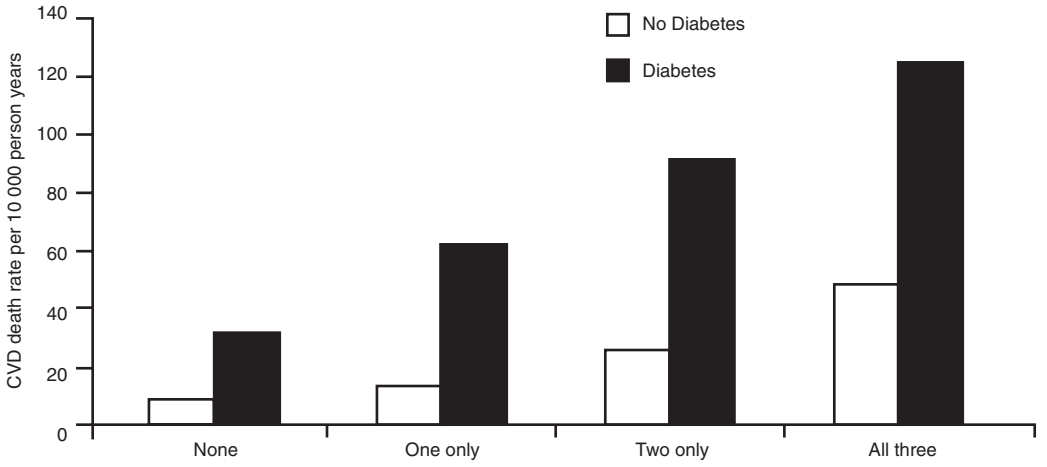

Figure 1 Age-adjusted cardiovascular death rates using a number of risk factors for men screened in the MRFIT trial with and without diabetes at baseline. Risk factors included serum cholesterol >200 mg/dl, smoking, and systolic blood pressure >120 mmHg. (Reproduced with permission from Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor intervention trial. *Diabetes Care* 1993; **16**: 434–44.)

Table 1 Lipid coagulation and fibrinolytic abnormalities seen in diabetes associated with increased cardiovascular risk.

1.	Elevated plasma levels of VLDL, LDL, and lipoprotein(a)
2.	Decreased plasma HDL cholesterol
3.	Increased lipoprotein oxidation
4.	Increased lipoprotein glycation
5.	Increased small dense LDL cholesterol
6.	Decreased lipoprotein lipase activity
7.	Elevated plasma levels of factor VII and VIII
8.	Increased fibrinogen and PAI-1 levels
9.	Elevated thrombin-antithrombin complexes
10.	Decreased antithrombin III, protein C and S levels
11.	Decreased plasminogen activators and fibrinolytic activity

thesis plays an important role in the development of mesangial hyperplasia and left ventricular hypertrophy in diabetes.[11]

Coagulation abnormalities in diabetes

A procoagulant state often exists in people with diabetes,[12,13] (Table 1). There is an increase in a number of coagulation factors such as PAI-1, von Willebrand's factor, fibrinogen, factor VII, and thrombin-antithrombin complexes, particularly in poor glycemic control conditions.[14] Plasma levels of lipoprotein(a) are elevated in diabetics with poor glycemic control,[15] which delay thrombolysis by inhibiting fibrinolysis and contribute to plaque progression.[16] There is also a decrease in the levels of antithrombin III and protein C, which impairs fibrinolysis in the diabetic state.[17] By improving glycemic control, the levels of antithrombin III and protein C increase, which enhances fibrinolysis activity.[16,17]

Platelet abnormalities

Platelet hyperactivity, aggregation, and adhesion to endothelial cells increases in association with diabetes, hypertension and accompanying macrovascular disease.[18] Platelets from people with diabetes have reduced membrane fluidity that is thought to be related to increased membrane cholesterol-to-phospholipid ratios.[19] Another process that likely contributes to enhanced platelet aggregation is an increase in glycosylation of platelet membrane proteins.[20] Furthermore, the dyslipidemia accompanying diabetes also contributes to enhanced platelet aggregation[21] (Table 2). Treatment strategies to reduce platelet aggregation are important for lowering CVD risk in these patients.[22,23]

Endothelial dysfunction and oxidative stress

Functional and anatomical abnormalities of the vascular endothelium are commonly associated with diabetes[24,25] (Table 3). Hyperglycemia results in the impairment of endothelial cell nitric oxide (NO) production, perhaps via activation of protein kinase C in endothelial cells, which predispose to increased production of vasoconstrictor prostaglandins, endothelin, glycated proteins, endothelial adhesion molecules, and platelet and vascular growth factors. These changes cumulatively enhance vasomotor tone and vascular permeability, growth and remodeling.[25] Further, hyperglycemia enhances endothelial cell matrix production, which may contribute to basement membrane thickening.[26] Elevation in tissue angiotensin II in diabetes may lead to increased oxygen radical production in cardiovascular tissues, which, in addition to reducing the half-life of NO, promotes oxidation of lipoproteins and other proteins of the heart, vascular system, and kidneys.[27] Thus,

Table 2 Abnormalities of platelet function in diabetes.

1.	Increased platelet adhesiveness
2.	Increased platelet aggregation
3.	Decreased platelet survival
4.	Increased platelet generation of vasoconstrictor prostanoids
5.	Reduced platelet generation of prostacyclin and other vasodilator prostanoids
6.	Altered platelet divalent cation homeostasis (i.e. decreased $[Mg^{2+}]_i$ and increased $[Ca^{2+}]_i$)
7.	Increased non-enzymatic glycosylation of platelet proteins
8.	Decreased platelet polyphosphoinositide content
9.	Decreased platelet production of nitric oxide
10.	Increased platelet myosin light-chain phosphorylation

Table 3 Alterations in vascular endothelium associated with diabetes.

1.	Elevated plasma levels of von Willebrand factor
2.	Elevated expression, synthesis, and plasma levels of endothelin-1
3.	Diminished prostacyclin release
4.	Increased destruction of NO and reduced responsiveness to NO
5.	Impaired fibrinolytic activity
6.	Increased endothelial cell procoagulant activity
7.	Increased endothelial cell surface thrombomodulin
8.	Impaired plasmin degradation of glycosylated fibrin
9.	Increased levels of advanced glycosylated end products
10.	Increased superoxide anion generation
11.	Increased vascular permeability
12.	Impaired vascular reactivity

treatments that lower tissue angiotension II levels, such as ACE inhibitors or angiotensin II blockers, may retard this process in diabetics, in whom there is an inordinate degree of cardiovascular oxidant stress.

Hypertension and diabetes

High blood pressure is about twice as frequent in people with diabetes as it is in those without the disease. Information from death certificates indicates that hypertension is implicated in a significant number of deaths coded to diabetes, and diabetes is involved in 10% of deaths coded to hypertension-related disease.

Up to 75% of diabetes-related cardiovascular complications may be attributable to hypertension, which in people with diabetes manifests certain unique and perplexing characteristics. Many diabetic patients lose their normal nocturnal drop in blood pressure,[28] which may reflect autonomic dysfunction and/or abnormal renal–neural sensing of the volume–pressure status. This observation has important practical implications. First, any blood pressure reading in the health care provider's office will likely underestimate the 24-h integrated pressure load on the cardiovascular system and kidneys.

Secondly, disproportionate elevations of blood pressure, especially systolic blood pressure, may enhance cardiovascular disease risk and the progression of renal disease in diabetic patients.[29] Because ambulatory blood pressure monitoring is not practical in most patients, home blood pressure measurements are often helpful.

Hypertension in diabetes is usually characterized by sodium and fluid retention and increased peripheral vascular resistance. Isolated systolic hypertension is more common in diabetic people, even at a relatively young age.[30]

Supine hypertension with orthostatic hypotension is not uncommon in diabetic patients with autonomic neuropathy. Standing blood pressure measurements should therefore be obtained at each office visit. Blood pressure tends to be more labile in people with diabetes, necessitating additional measurements over a longer period to establish the representative blood pressure.

An increased propensity for orthostatic hypotension renders alpha-adrenergic blocking agents to second-line therapy in this population. In addition, doses of all antihypertensive agents must be titrated more carefully in diabetic hypertensive patients with a greater propensity for orthostatic hypotension.

Finally, diabetic nephropathy, which occurs in 20% of those with type 2 diabetes and one-third of those with type 1 diabetes, also promotes the development and progression of hypertension.

Treatment and prevention of macrovascular complications in diabetes

The goal of lowering blood pressure in people with diabetes and hypertension is to prevent the hypertension-associated death and disability in this population.[31] Therapy should begin with lifestyle modifications (Table 4) involving weight reduction, increased physical activity and moderation of dietary salt and alcohol intake. If the target BP of 130/85 mmHg is not achieved, as in the case of most diabetic patients, then pharmacologic intervention is indicated.

Based on clinical trial results, four classes of drugs are effective and appropriate first-line therapy in diabetic patients. Most diabetics will require the use of several different agents to achieve a therapeutic goal of 130/85 mmHg.[32] Often, a low-dose diuretic is needed as part of combination therapy in order to accomplish goal blood pressure (Figure 2).

ACE inhibitors have been recognized as first-line antihypertensive therapy in diabetic people with proteinuria.[33] Further, as proteinuria is a harbinger for CVD as well as renal disease,[34] these agents may also afford unique benefits in preventing CVD and diabetic nephropathy. In fact, the result of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial suggested a cardioprotective effect of ACE inhibitors.[35] Further, the Heart Outcomes Prevention Evaluation Study Investigators found that Ramipril (ACE inhibitor) reduces the rate of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.[36] However, in the UK Prospective Diabetes Study Group report, blood pressure lowering with an atenolol-based program was similarly effective as a captopril-based regimen in reducing the incidence of diabetic complications both micro- and macrovascular. Reductions in risk in the group assigned to tight blood pressure control (144/82 mmHg) were 24% in diabetes-related end points, 32% in deaths related to diabetes, 44% in strokes, and 37% in microvascu-

Table 4 Lifestyle modifications for hypertension prevention and management.

• Lose weight, if overweight
• Limit alcohol intake to no more than 1 oz (30 ml) of ethanol (e.g. 24 oz of beer, 10 oz of wine, or 2 oz of 100 proof whiskey) per day, or 0.5 oz of ethanol per day for women and lighter weight people
• Increased aerobic physical activity (30–45 min most days of the week)
• Reduce sodium intake to no more than 100 mmol/d (2.4 g of sodium or 6 g of sodium chloride)
• Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
• Maintain adequate intake of dietary calcium and magnesium for general health
• Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health

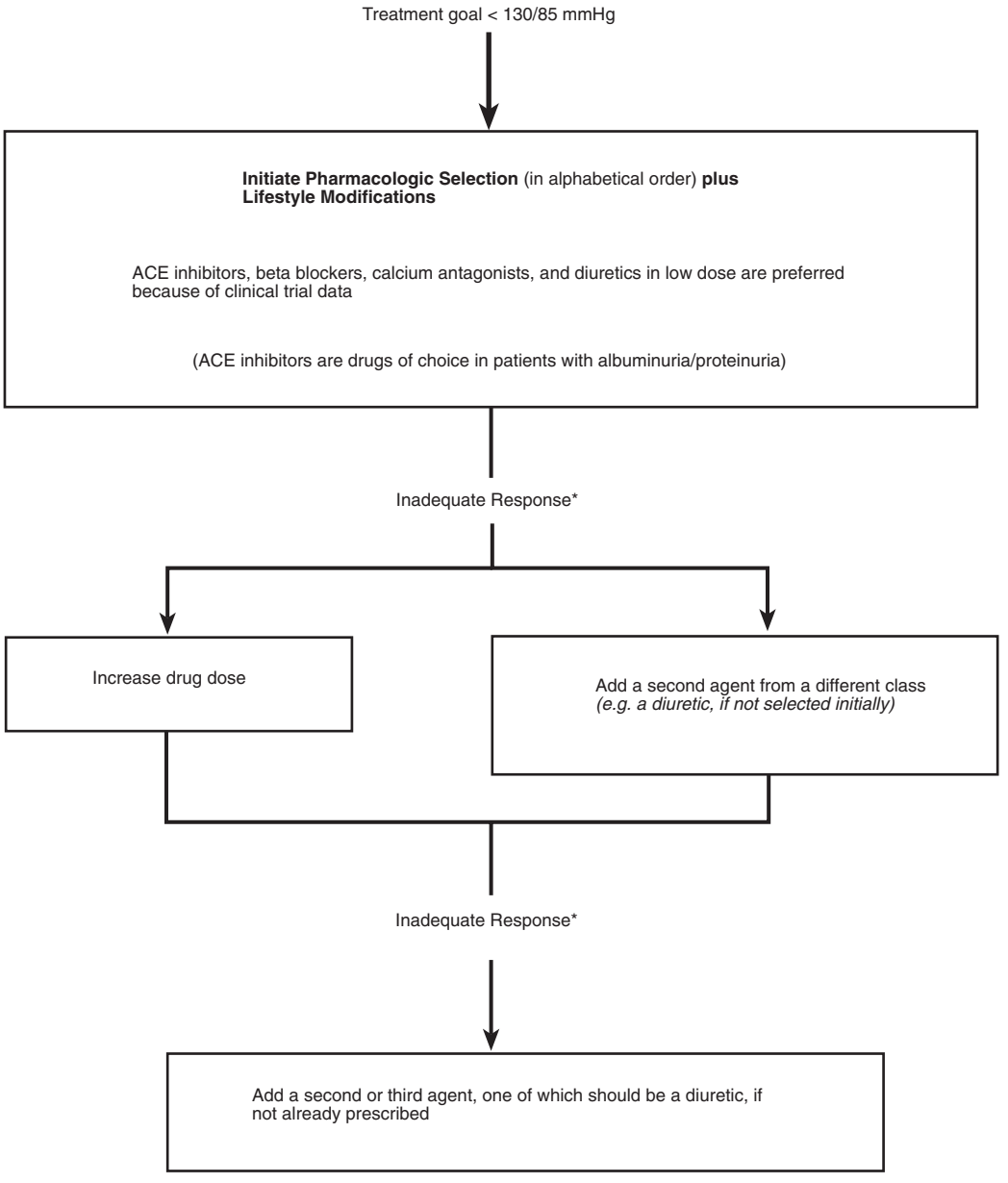

Figure 2 Algorithm for the treatment of hypertension in diabetic people. *An adequate response means goal blood pressure achieved or considerable progress. (ACE, angiotensin-converting enzyme.)

lar end points, especially diabetic retinopathy. These results suggest that combination therapy, which includes either an ACE inhibitor or a β-blocker, is very effective in reducing macro- and microvascular events as long as blood pressure is adequately lowered. Moreover, the relative benefit on CVD risk reduction is conferred in a far more powerful fashion by intensive blood pressure reduction versus intensive blood glucose control.[37–39]

Results of the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) suggest that the combination of an ACE inhibitor and a calcium antagonist may be beneficial in reducing CVD in patients with type 2 diabetes and hypertension. The incidence of CVD events was less in the fosinopril than in the amlodipine treatment groups, but the incidence was least in the group that received both agents (Figure 3).

These data suggest that the addition of a calcium antag-

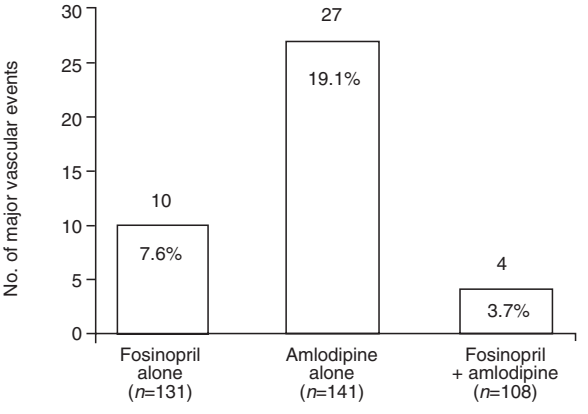

Figure 3 Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET): major cardiovascular events according to treatment.

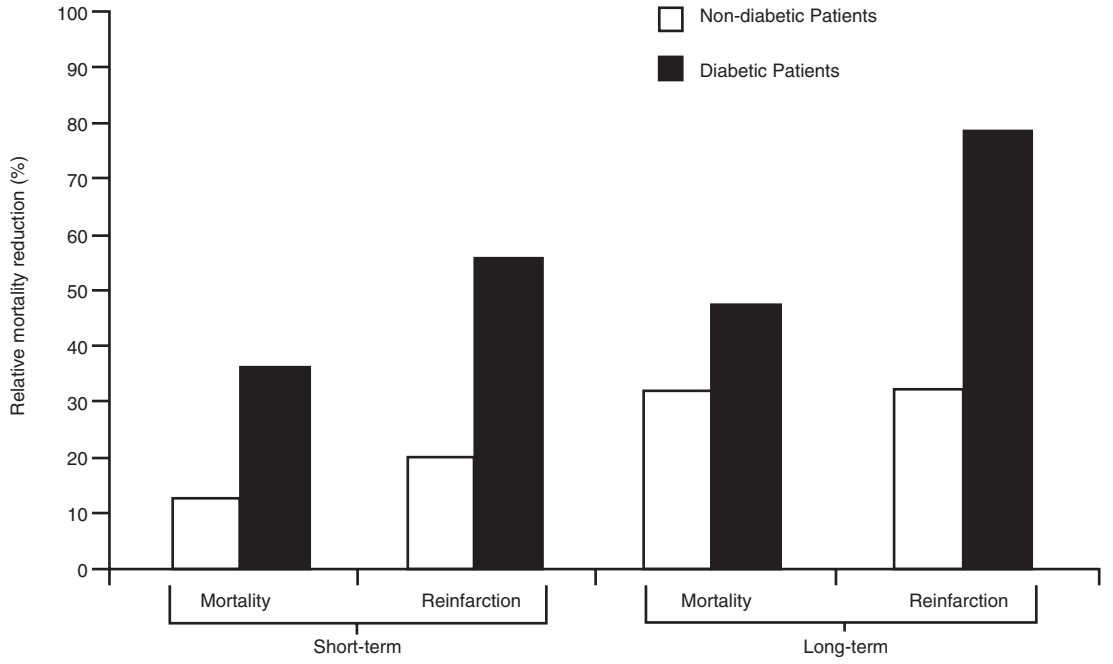

Figure 4 Effect of beta-blocker therapy on mortality and reinfarction rates in patients with and without diabetes after myocardial infarction, expressed as a percentage reduction compared with patients receiving placebo. (Reproduced with permission from Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. *Ann Intern Med* 1995; **123**: 358–67.)

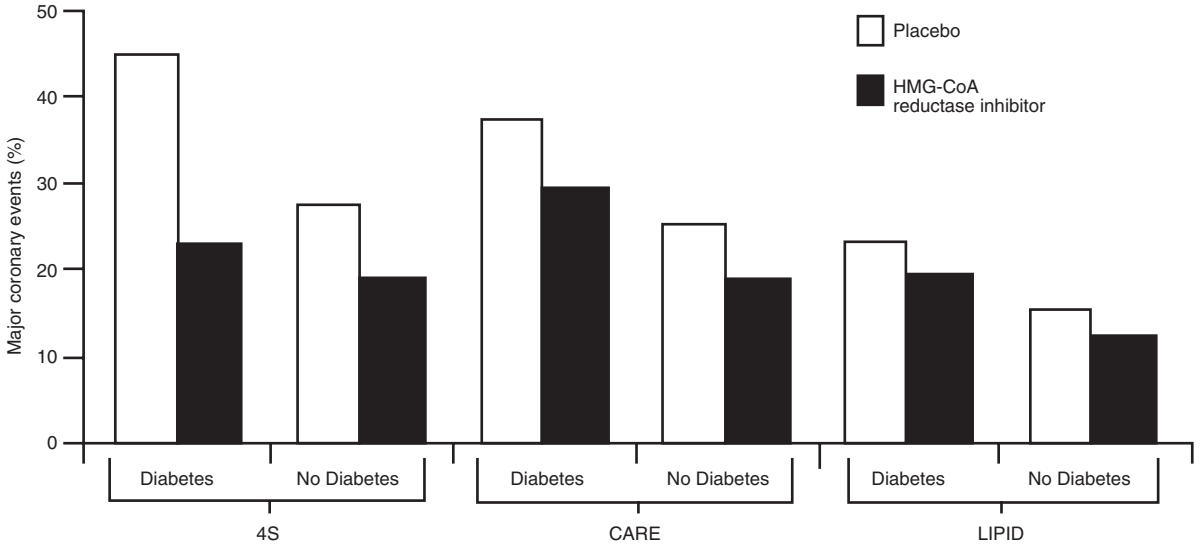

Figure 5 Effect of lipid-lowering therapy with statins on the rate of major coronary events in patients with and without diabetes after myocardial infarction. (4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol And Recurrent Events study; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease.)

onist to baseline ACE inhibitor therapy is a good strategy for treatment of hypertension in diabetics but that ACE inhibitors may be more beneficial than a calcium antagonist as initial therapy.[40] Thiazide diuretics, in relatively low doses (25 mg or less of hydrochlorothiazide daily), are effective and safe antihypertensive agents in patients with diabetes.

In the Systolic Hypertension in the Elderly Program (SHEP) study, elderly men with type 2 diabetes derived as much benefit, in terms of stroke and ischemic heart disease reduction, as those without diabetes.[41]

Diuretics in low doses are not generally associated with significant metabolic abnormalities. Use of diuretics in conjunction with ACE inhibitors often produces synergistic effects, allowing reduced diuretic dosages to minimize the potential metabolic problems. Furthermore, diuretics are often required for hypertensive diabetics to counteract the salt sensitivity and expanded plasma volume frequently seen in these patients. This is particularly relevant as several drugs are often required to control blood pressure levels of $<$130/85 mmHg in these patients. An analysis of clinical trials,[32] suggested that, on average, diabetic patients require three to five different classes of antihypertensive medications to achieve blood pressure levels $<$130/85.

Results from the subset analysis of type 2 diabetics in the Hypertension Optimal Treatment (HOT) trial[42] suggest that further reduction in diastolic blood pressure <85 mmHg is beneficial. The special benefits of aggressive blood pressure lowering in the diabetic population was observed in a recent subanalysis of this cohort in the Syst-Eur trial. In this trial, while systolic blood pressure was reduced by a comparable amount in each group (–22 ± 16 mmHg, non-diabetics versus –22.1 ± 14 mmHg, diabetic group), the risk reduction in mortality from CVD was 13% for the non-diabetics and 76% for the diabetic patients. Thus, the benefit conferred per mmHg blood pressure reduction appears to be greater in patients with type 2 diabetes than in those with hypertension but no coexistent diabetes.

Beta-blockers are the drugs of choice for post-infarction therapy in diabetic as well as non-diabetic individuals[33] (Figure 4). They are also useful as adjunct and combination antihypertensive therapy in these patients. However, it should be kept in mind that β-blockers may have adverse effects on glucose and lipid metabolism, and in combination with calcium antagonists may cause bradycardia and heart block. Also β-blockers may be beneficial in the treatment of diabetics who demonstrate supine hypertension with orthostatic hypotension because they do not produce vasodilatation.

Alpha-blockers may also be useful for combination antihypertensive therapy in patients with diabetes.[33] They do not have adverse effects on glucose metabolism or lipid profile. However, these drugs must be administered with care in diabetics because of their propensity to augment orthostatic hypotension,[29] and their propensity to increase the development of heart failure in a high-risk populations.

The dyslipidemia in diabetics is associated with a worse prognosis than in an isolated increase in LDL cholesterol and is more difficult to treat.[43] Furthermore, a reduction in LDL cholesterol in diabetics is associated with at least as great a reduction in CVD risk as seen in people without diabetes. For example, subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) trial in a cohort of 201 type 2 diabetic patients suggested that the absolute CVD risk reduction was greater in the diabetic cohort than in the non-diabetic group.[44] Subgroup analysis of the Cholesterol And Recurrent Events (CARE) study[45] also showed similar results. Given the fact that type 2 diabetics are at the same risk as non-diabetics who have had a myocardial infarction or stroke, and the greater atherogenicity of their LDL particles (small, dense, oxidized, glycated), it is generally recognized that LDL should be lowered to levels <100 mg/dl[44] (Figure 5).

Finally, patients with diabetes should receive 325 mg of aspirin daily[22] unless an absolute contraindication exists. Data from the Antiplatelet Trialists' Collaboration[23] indicated that the greatest reduction in CVD was achieved with a dose between 165 and 325 mg/day for high-risk patients such as those with diabetes.

Summary

Diabetes mellitus is a major risk factor for CVD, and aggressive therapy for its manifestations (dyslipidemia, hypertension and platelet dysfunction) is indicated in order to prevent the high mortality rate associated with macrovascular complications.

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