Primary and Secondary Prevention Strategy for Cardiovascular Disease in Diabetes Mellitus

Sundararajan Srikanth, MDa, Prakash Deedwania, MDb,*

Diabetes is a metabolic and a vascular disease manifested by arterial inflammation and endothelial dysfunction leading to micro- and macrovascular pathology. Type 2 diabetes has reached worldwide epidemic proportions. By the year 2025 the number of individuals with diabetes mellitus in the world is expected to exceed 350 million with a prevalence of 4.4%.1 Diabetes continues to affect a substantial proportion of the adult population in the United States. From the National Health and Nutrition Examination Survey (NHANES) 1999/2000 data,2 8.3% of persons aged 20 years or more had either diagnosed or undiagnosed diabetes, and this percentage increased to 19.2% for persons aged 60 years or more in the United States. Men and women were affected similarly by diabetes. In 1999/2000, an additional 6.1% of adults had impaired fasting glucose, increasing to 14.4% for persons aged 60 years or more; men were affected more than women.3 Overall, an estimated 14.4% of the US population aged 20 years or more and 33.6% of those aged 60 years or more had either diabetes or impaired fasting glucose. In the last decade, type 2 diabetes has also been diagnosed more frequently in children and adolescents concomitant with the increasing prevalence of obesity and decreased physical activity in this population.

Cardiovascular (CV) diseases are the leading cause of morbidity and mortality in the general population. Haffner and colleagues4 initially reported that patients with type 2 diabetes without a history of myocardial infarction (MI) have the same risk of coronary artery disease (CAD) as those without diabetes with a history of MI. Subsequently the National Cholesterol Education Program stated that diabetes is considered a coronary heart disease (CHD) risk equivalent.5 The baseline risk of CV disease is multiplied 2- to 4-fold in persons with diabetes mellitus with a higher case fatality rate compared with patients without diabetes.6 There are a few articles questioning the conclusion that the diabetic state confers CV risk equivalent to that of preexisting CAD. The most recent article based on data from the REACH registry suggests that the CV risk of a person with diabetes without additional risk factors lies in between that of an individual without diabetes and someone with established CV disease.7 However, the diabetic cohort in the REACH registry had a much greater

---

KEYWORDS

• Diabetes mellitus • Cardiovascular disease • Primary prevention

---

a Division of Cardiology, VACCHCS/CMC, UCSF Program at Fresno, Fresno, CA, USA
b Division of Cardiology, Department of Medicine, Veterans Affairs Central California Health Care System/University of California, San Francisco, Fresno Program, 2615 East Clinton Avenue, Fresno, CA 93703, USA
* Corresponding author. Division of Cardiology, Department of Medicine, Veterans Affairs Central California Health Care System/University of California, San Francisco, Fresno Program, 2615 East Clinton Avenue, Fresno, CA 93703.
E-mail address: deed@fresno.ucsf.edu

Cardiol Clin 29 (2011) 47–70
doi:10.1016/j.ccl.2010.11.004
0733-8651/11/$ – see front matter. Published by Elsevier Inc.
adherence to statin therapy, which explains the lower event rates. Recent data from the Danish population study and the million women study from Europe, both of which were prospective long-term studies in the general population, show that in the diabetic cohort who are not on statin therapy the risk of CV disease is equivalent to that of an individual without diabetes but with known CAD.\mbox{\textsuperscript{6,9}} Moreover a recent meta-analysis of individual records from studies in the Emerging Risk Factors Collaboration involving nearly 700,000 individuals reported a doubling of risk for CAD as well as for stroke independent of other conventional risk factors in the presence of diabetes mellitus thus reinforcing the fact that the CV risk in the presence of diabetes approximates that of CV risk in the individual with prior ischemic coronary event.\mbox{\textsuperscript{10}}

CV disease accounts for 65\% of deaths in persons with type 2 diabetes mellitus. Much of the morbidity and mortality is from atherosclerotic CAD, congestive heart failure and sudden cardiac death. Advances in medical therapy, interventional techniques and surgical techniques have resulted in only modest improvements in mortality from CV disease in men with diabetes and in fact mortality rates during the last decade have risen for women with diabetes and CV disease (\textbf{Fig. 1}).\mbox{\textsuperscript{11}}

The excess CV mortality and morbidity in the diabetic population reflects the general vascular inflammation that is seen in this disease state. Significant progress has been made in elucidation of the mechanism and consequences of the metabolic perturbations in the diabetic state. The disease is characterized by insulin resistance and is commonly associated with the metabolic syndrome. Sensitivity to insulin is variable in the population at large. Insulin resistance develops as a result of a complex interplay of genetic and environmental factors. Hyperinsulinemia occurs as an adaptive response to increasing insulin resistance.

![Fig. 1. Change in age-adjusted 8- to 9-year CV mortality in NHANES for 30 years. (Data from Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999;281:1291–7.)](image)

**PATHOGENESIS OF TYPE 2 DIABETES MELLITUS**

Type 2 diabetes develops when insulin-resistant individuals cannot maintain the degree of excess insulin secretion needed to overcome insulin resistance. The development of the overt diabetic condition is preceded by a prediabetic phase which usually lasts 6 to 8 years (\textbf{Fig. 2}). The prediabetic milieu is characterized by hyperinsulinemia, hypertension, and endothelial dysfunction. Insulin resistance and hyperglycemia seem to set the stage for the development of the metabolic syndrome characterized by dyslipidemia, endothelial dysfunction, hypercoagulability, hypertension, and truncal obesity, which is present in approximately 25\% of adults in the United States.\mbox{\textsuperscript{12}} The metabolic syndrome also known as the insulin resistance syndrome or cardiovascular dysmetabolic syndrome (CDS), is a constellation of metabolic abnormalities that are associated with a higher risk of CV disease and mortality.\mbox{\textsuperscript{13}} The metabolic risk factors for CV disease that make up the metabolic syndrome do not directly cause type 2 diabetes but are frequently associated with it (\textbf{Table 1}). Multiple prospective observational studies demonstrate a strong association between the metabolic syndrome and the risk for subsequent development of type 2 diabetes.\mbox{\textsuperscript{14}} The risk of diabetes seems to increase with increasing components of the metabolic syndrome.\mbox{\textsuperscript{15}}

Both type 2 diabetes and CV disease stem from a complex interaction of insulin resistance and visceral obesity. Clearly environmental factors in the form of excess calorie intake contribute significantly to the genesis of type 2 diabetes in addition to genetic tendencies. Visceral adipose tissue acts as an endocrine factory releasing various adipokines with effects on the vascular, hepatic, and muscular tissues (\textbf{Fig. 3}). Positive energy balance in the adipose tissue may mediate insulin resistance by lipotoxicity in various tissues. Free fatty acids inhibit insulin-stimulated peripheral glucose uptake while promoting the development of dyslipidemia, characterized by low high-density lipoprotein-cholesterol (HDL-C), high triglycerides, and increased small dense low-density lipoprotein-cholesterol (LDL-C). Other adipokines promote systemic inflammation, and increase oxidant stress promoting thrombosis. These effects interfere with the normal function of the vascular endothelium, and result in reduced nitric oxide bioavailability followed by disruption of the structural integrity of the endothelial monolayer. This break in the integrity of the endothelium allows entry of LDL-C in the media, which on further modification by oxidation and monocyte ingestion leads to the formation of the classic foam cells. Accumulation of foam cells...
leads to the formation of fatty streaks that are classically believed to lead to atherosclerosis.

The approach to management of the patient with diabetes should prioritize the goal of reducing CV morbidity and mortality while also addressing microvascular complications (nephropathy and retinopathy). For this to transpire, interventions should be targeted at the basic pathophysiologic processes that have been identified as risk factors leading to atherosclerosis and CV disease and are manifest more aggressively in the patient with diabetes (Box 1). In the following sections, the current literature pertaining to individual risk factor intervention for primary and secondary prevention of CV disease in the patient with diabetes is briefly reviewed. The rationale for a comprehensive risk reduction strategy based on available data is emphasized.

**SIGNIFICANCE AND TREATMENT OF INDIVIDUAL RISK FACTORS IN TYPE 2 DIABETES MELLITUS**

**Dyslipidemia**

Hypertriglyceridemia was one of the first metabolic abnormalities recognized to be associated with insulin resistance. The mechanism of hypertriglyceridemia is understood to be caused by differential insulin sensitivity of the tissues in the individual’s body. Defects in the ability of insulin to mediate muscle use of glucose and inhibit lipolysis in adipose tissues seem to be the primary

---

**Table 1**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity (waist circumference)</td>
<td>Europid men &gt;94 cm (south Asian &gt;90 cm), Europid and south Asian women &gt;80 cm</td>
</tr>
<tr>
<td>Plus any 2 of the following</td>
<td></td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>$\geq 1.7$ mmol/L or on specific treatment for this abnormality</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>Men &lt;1.03 mmol/L, women &lt;1.29 mmol/L, or on specific treatment for this abnormality</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic BP $\geq 130$ mm Hg, or diastolic BP $\geq 85$ mm Hg or on specific treatment for this abnormality</td>
</tr>
<tr>
<td>Abnormal glycoregulation</td>
<td>Fasting plasma glucose $\geq 5.6$ mmol/L, or previously diagnosed type 2 diabetes mellitus</td>
</tr>
</tbody>
</table>

*Abbreviation: BP, blood pressure.*

abnormalities that cause the insulin-resistant state.\textsuperscript{16} The resistance at the level of the muscle and adipose tissue leads to persistently higher ambient levels of insulin and free fatty acids. In response to the higher free fatty acid level, the hepatic tissue increases the rate of conversion of free fatty acids to triglycerides. This is accentuated by the normal insulin sensitivity of the hepatic tissues in the face of compensatory hyperinsulinemia. The appreciation of the difference in the insulin sensitivity of the various tissues has led to better understanding of the abnormalities caused by insulin resistance. Although the classic diabetic dyslipidemia is characterized by high serum triglyceride levels, low levels of HDL-C and an increased number of small dense LDL particles, there are additional lipid abnormalities as well.\textsuperscript{17,18} LDL-C is the major cholesterol-rich lipoprotein that mediates the link between serum cholesterol and atherosclerosis. The interaction of LDL-C with monocytes transforms them into the foam cells that are seen in atherosclerotic LDL plaques. This interaction of the monocytes with LDL occurs only when the LDL is modified by acetylation, oxidation, or glycosylation as realized in diabetes mellitus. Moreover the small dense LDL particles that are abundant in diabetes mellitus are particularly atherogenic.\textsuperscript{19} Thus, quantitative and qualitative lipid abnormalities mediate the increased risk of atherosclerosis in diabetes mellitus as shown by the MRFIT and United Kingdom Prospective Diabetes Study (UKPDS)\textsuperscript{20,21} data. Evaluation of the importance of various risk factors for CAD in UKPDS shows that LDL-C and HDL-C are the best predictors of CHD (\textit{Table 2}).

In the diabetic population the prevalence of hypertriglyceridemia and low HDL-C levels is approximately twice as high and the prevalence of high LDL-C levels is not different compared with the nondiabetic population.\textsuperscript{22} However whatever the amount of LDL-C in the diabetic individual, the LDL is atherogenic (type B small dense LDL) and therefore treatment with statins has been found to be highly effective in preventing macrovascular events. Initial data on the benefits of statins in patients with diabetes were obtained from subgroup analyses of the major secondary intervention trials such as the Scandinavian Simvastatin Survival Study (4S) and CARE trials.\textsuperscript{23,24} In the 4S study, simvastatin led to a 35\% decrease in LDL-C resulting in a 42\% decrease in the incidence of nonfatal MI and CV mortality. A meta-analysis of the CARE (Cholesterol and Recurrent Events) and LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) studies showed a 25\% decrease in incidence of major coronary events and revascularizations in the subgroup of patients with diabetes.

---

\textbf{Box 1}

\textbf{Cardiac risk factors in type 2 diabetes}

- Hyperglycemia
- Hypertension
- Atherogenic dyslipidemia
- Increased platelet aggregation
- Increased plasminogen activator inhibitor-1
- Increased thrombogenicity
- Increased fibrinogen level
- Increased von Willebrand factor
- Decreased tissue plasminogen activator

---

\textbf{Fig. 3.} Adipocyte role in insulin resistance, metabolic syndrome, and CV disease. (\textit{From} Deedwania PC, Volkova N. Current treatment options for the metabolic syndrome. \textit{Curr Treat Options Cardiovasc Med} 2005;7:63; with permission.)

---
More recently the benefits of high-dose statins were shown in the Treating to New Targets (TNT) study, which compared atorvastatin 80 mg/d to 10 mg/d in patients with stable CAD. A subanalysis showed that major CV events were reduced by 25% in patients with diabetes receiving high-dose atorvastatin supporting the use of intensive lipid-lowering regimens (Fig. 4). Further post hoc analysis of the TNT study was done to investigate the effect of intensive lipid lowering on future CV events in patients with diabetes, with or without coexisting mild to moderate chronic kidney disease (CKD). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced the relative risk of major CV events by 35% in patients with diabetes and CKD and by 10% in patients with diabetes and normal estimated glomerular filtration rate. The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major CV event in 4.8 years (Fig. 5). This result is very encouraging and is in contrast to previous observations in patients with diabetes and end-stage renal disease.

These data from the TNT analysis of the diabetic cohort provide strong support for the prevailing recommendations of reducing LDL-C to levels less than 70 mg/dL as recommended by various guidelines including the American Diabetes Association (ADA). From the TNT data, further reduction of LDL-C with intensive statin therapy provided no safety concerns in patients with diabetes and diabetes along with CKD. It is instructive to look at some of the other secondary prevention trials preceding the TNT trial (Fig. 6).

In the diabetic cohort of the 4S study, LDL-C decreased from a mean of 186 mg/dL to 119 mg/dL (36% reduction) on simvastatin with a 55% reduction in CHD. In the diabetic cohort of the LIPID trial, the LDL changed from a mean of 150 mg/dL to 112 mg/dL on pravastatin with a 19% risk reduction in CHD. The CARE cohort started with a mean LDL of 136 mg/dL, which decreased to 98 mg/dL with a 25% risk reduction in CHD on pravastatin. In the Health Protection Study, mean LDL decreased from 127 to 89 mg/dL (30% reduction) with a 21% reduction in CHD events. The results of the post hoc analysis of the diabetic subgroup from TNT

Table 2
Stepwise selection of risk factors in 2693 diabetics with time to first event as dependent variable: UKPDS CAD (n = 280)

<table>
<thead>
<tr>
<th>Position in Model</th>
<th>Variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>LDL-C</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Second</td>
<td>HDL-C</td>
<td>0.0001</td>
</tr>
<tr>
<td>Third</td>
<td>Hemoglobin A1c</td>
<td>0.0022</td>
</tr>
<tr>
<td>Fourth</td>
<td>Systolic BP</td>
<td>0.0065</td>
</tr>
<tr>
<td>Fifth</td>
<td>Smoking</td>
<td>0.056</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex.


Fig. 4. Time to first major CV event in all patients with diabetes: TNT trial. (Data from Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006;29:1220–6.)
extend this linear declining trend seen in the CHD event rates with declining LDL-C levels, similar to the results seen in the overall study. End-of-treatment mean LDL-C levels were 98.6 mg/dL with atorvastatin 10 mg and 77.0 mg/dL with atorvastatin 80 mg in the TNT cohort. These data show that by aggressive LDL-C reduction, between the 4S placebo group and the TNT atorvastatin 80 mg group, statin therapy alone was able to achieve a 70% reduction of CHD events. Thus, the target LDL-C for secondary prevention of CHD in the setting of diabetes should be 70 mg/dL. Moreover, aggressive reduction of LDL-C should be sought in this population from the outset.

Although the studies mentioned earlier included only diabetic patients with established CHD, the findings from the Heart Protection Study support the use of lipid-lowering therapy in diabetes without clinically evident atherosclerotic disease.27 This study, which included almost 4000 people with diabetes without prior CHD, demonstrated a 26% risk reduction of nonfatal MI, CV death, stroke, or revascularizations in the group of subjects treated with simvastatin 40 mg/d (Fig. 7).

The Collaborative Atorvastatin Diabetes Study (CARDS), involving patients with type 2 diabetes, was halted 2 years early because patients allocated to atorvastatin had significant reduction (37%) in combined CV end points compared with those receiving placebo (Fig. 8).28 In this primary prevention study, 2838 persons with type 2 diabetes between the ages of 40 and 75 years with no previous history of CHD, stroke, or other major CV events and a documented history of at least 1 of retinopathy, micro-/macroalbuminuria, hypertension or current smoking, LDL equal to or less than 4.14 mmol/L (160 mg/dL), and triglycerides equal to or less than 6.78 mmol/L (600 mg/dL) were randomized to either placebo or atorvastatin 10 mg daily. Patients who received 10 mg daily of atorvastatin had a 37% reduction in major CV events such as acute MI, stroke, angina, and revascularization compared with control patients. This was a landmark trial that was designed specifically to answer the question of primary prevention of micro- and macrovascular disease in the diabetic population. Treatment with atorvastatin resulted in benefit even in individuals with LDL
levels lower than 100 mg/dL at the time of initiation of the medication.

Although there is a great deal of evidence supporting the use of statins in diabetics for CV risk reduction, there is less evidence for interventions directed at diabetic dyslipidemia (high triglyceride and low HDL). The fibrate class of lipid-lowering drugs is useful for lowering increased triglyceride or non–HDL-C levels. However, clinical trial data with these drugs have shown mixed results. The Helsinki Heart Study involved 135 patients with type 2 diabetes without concurrent CVD. A 68% relative risk reduction in coronary death and nonfatal MI was seen in association with a 10% reduction in LDL and 26% reduction in triglycerides with gemfibrozil 600 mg twice a day. However, this result did not reach statistical significance because of the small sample size. The FIELD trial randomized 9795 individuals with type 2 diabetes at risk

---

**Fig. 7.** Health Protection Study diabetes substudy: absolute effects on 5-year rates of first major vascular event. (Adapted from Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005–16; with permission.)

**Fig. 8.** Collaborative Atorvastatin Diabetes Study (CARDS). Cumulative hazard of primary end point, all-cause mortality, and any cardiovascular end point for heterogeneity. (Data from Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.)
for CAD to either fenofibrate 200 mg/d or placebo. Statins and other lipid-lowering therapy were allowed any time after randomization. There was no difference in the primary composite end point of CHD death or nonfatal MI. The secondary composite end point of total CV disease events was lower in the fenofibrate group (12.5% vs 13.9%, \( P = .035 \)), primarily because of a reduction in nonfatal and coronary revascularization. Patients in the placebo group were more frequently treated with other lipid-lowering therapy, predominantly statins, during the 5-year follow-up, which may have negated any treatment effect differences between the fenofibrate and placebo groups.

The ACCORD Lipid trial evaluated treatment with fenofibrate compared with placebo among patients with type 2 diabetes treated with an open-label statin medication. Among the 5518 patients randomized into the study, the addition of fenofibrate to statin therapy was not superior to statin therapy alone. Although fenofibrate reduced triglyceride levels, there was only a small difference in mean HDL and no difference between LDL-C between groups, which could help to explain lack of benefit (Fig. 9).

However, most subjects in the ACCORD study treated with fenofibrate did not have increased triglyceride or low HDL-C. Those subjects with residual atherogenic dyslipidemia as identified by an increased triglyceride level and low HDL-C had a significant 31% reduction in primary end point (first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes). The risk associated with atherogenic dyslipidemia was 17.3%, which is comparable with the risk in individuals with prior CV disease. This finding is consistent with the results of previous studies using fibric acid derivatives (Fig. 10). Thus, although the overall ACCORD lipid trial seems to be negative, subgroup analysis would suggest that there is value to adding fenofibrate to a statin in diabetic individuals with residual risk arising from atherogenic dyslipidemia.

To summarize, the goals of therapy as recommended by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program include a LDL-C target of less than 100 mg/dL; serum triglyceride level less than 150 g/dL and HDL-C greater than 40 mg/dL. The panel also recommends a secondary target of therapy in non–HDL-C (total cholesterol minus HDL-C). In diabetic individuals with a triglyceride level greater than or equal to 200 mg/dL, the non–HDL-C goal is 130 mg/dL. The choice of a particular agent depends on the baseline lipid profile. If baseline LDL-C is less than 100 mg/dL, statin therapy should be initiated based on risk factor assessment. A statin is the drug of choice if LDL-C is greater than 100 mg/dL. If triglycerides are equal to or greater than 500 mg/dL, treatment options include fibrates or niacin to lower triglyceride level before initiating LDL-lowering therapy. Although there is no official modification by the National Cholesterol Education Program (NCEP), a recent advisory from the NCEP as well as ADA guidelines suggests that because of the associated high risk of coronary events, the appropriate LDL target for the diabetic population may be 70 mg/dL.

However, in light of the FIELD and recent ACCORD lipid trials, the role of additional treatment with
fibrate to further improve the outcome is an open question.

**Hypertension**

Hypertension is seen in about 60% to 80% of individuals with type 2 diabetes. As with the metabolic syndrome this often predates the manifestation of overt diabetes. There is significant association between the blood pressure and insulin sensitivity.35,36 The mechanisms believed to mediate hypertension include insulin resistance and diabetic nephropathy. Insulin resistance and concurrent hyperinsulinemia possibly cause sodium retention by the kidneys, stimulate growth of vascular smooth muscle cells and affect endothelial function, vascular reactivity, and blood flow.

Several trials have been published regarding the treatment of hypertension in diabetes mellitus. They have shown beyond reasonable doubt that adequate control of blood pressure can protect against macrovascular and microvascular complications. In the Hypertension in Diabetes Study (a substudy of UKPDS), diabetic subjects were randomized into groups with different blood pressure control targets (Fig. 11). After a mean follow-up of more than 8 years there was a relatively greater decrease in diabetes-related mortality by 32%, stroke incidence by 44%, and congestive heart failure incidence by 56% in the aggressively treated group (mean blood pressure 144/82 mm Hg on treatment) compared with the less aggressively treated group (mean blood pressure of 154/87 mm Hg).37

The Hypertension Optimal Treatment (HOT) trial showed that targeting diastolic blood pressure to less than 80 mm Hg in patients with diabetes was associated with a 51% reduction of CV mortality in a 4-year period compared with the group with a target diastolic blood pressure of less than 90 mm Hg.38 If the diabetic subgroup was removed from the analysis, the benefit in the rest of the population did not achieve statistical significance. The ACCORD study randomized a total of 4733 patients with type 2 diabetes mellitus to intensive antihypertensive therapy with a target systolic pressure of less than 120 mm Hg (Fig. 11). The ACCORD subgroup results with those from prior fibrate studies (Data from Refs.29–31,86)

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (Gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG &gt; 200 mg/dl LDL-C/HDL-C &gt; 5.0</td>
<td>-71% (0.005)</td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 200 mg/dl</td>
<td>-39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 204 mg/dl HDL-C &lt; 42 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>TG ≥ 204 mg/dl HDL-C &lt; 34 mg/dl</td>
<td>-31%</td>
</tr>
</tbody>
</table>

Fig. 10. Comparison of ACCORD subgroup results with those from prior fibrate studies. (Data from Refs.29–31,86)
Hg or standard therapy for systolic pressure target less than 140 mm Hg. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard therapy group. At 1 year there was no difference in the primary composite outcome (nonfatal MI, nonfatal stroke, or death from CV causes). It should perhaps not come as a surprise that there was no improvement in the primary composite outcome because control of blood pressure to a value less than 130 mm Hg systolic has not been shown to improve coronary events in most studies. On the other hand, there is a close correlation between systolic blood pressure and risk of stroke rate down to a lower value of 115 mm Hg. In the ACCORD study, it was shown that decreasing systolic blood pressure down to a mean value of 119.3 mm Hg was associated with decrease in all strokes and nonfatal strokes (Fig. 12).\(^3\)

Results from the ADVANCE study are also instructive in the management of hypertension in the patient with diabetes.\(^4\) ADVANCE was a 2 \times 2 factorial study, in which 11,140 patients were randomized to either intensive glucose control or standard glucose therapy, and fixed-dose combination of perindopril and indapamide, or placebo. After a 6-week run-in phase with usual glucose control, patients who tolerated and complied with the blood pressure regimen were randomized to either intensive glucose control, or a strategy of standard glucose control. After a mean of 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned to control remained on randomized treatment. Compared with patients assigned to placebo, those who received active therapy had a mean reduction in systolic blood pressure of 5.6 mm Hg (mean systolic blood pressure of 134.7 mm Hg active vs 140.3 mm Hg placebo) and diastolic blood pressure of 2.2 mm Hg (mean diastolic blood pressure 74.8 mm Hg active vs 77 mm Hg placebo). The relative risk of death from CV disease was reduced by 18% (\(P = 0.03\)) and death from any cause was reduced by 14% (\(P = 0.03\)) (Fig. 13). This benefit was attributed mostly to reduction in microvascular events.

So the natural question that arises is what should be the target blood pressure for therapy in the patient with diabetes? Although guidelines have recommended target blood pressure less than 130/80 mm Hg or 120/75 mm Hg in those with CKD,\(^4\) this target had not been supported by prospective, large-scale, randomized controlled trials specifically designed to evaluate the benefit of targeted therapy to a goal of blood pressure less than 130/80 mm Hg. The ACCORD blood pressure study is the first such trial where treatment directed to a goal of less than 120/80 mm Hg was prospectively evaluated against a blood pressure goal of less than 140/80 mm Hg. Although the findings of the ACCORD trial have not yet been incorporated into guidelines, it seems reasonable in the meanwhile to consider that the target blood pressure for most patients with diabetes should be less than 130/85 mm Hg.

The other important take-home message from UKPDS and other trials is that adequate control of blood pressure generally requires the use of 2 or more antihypertensive agents.\(^4\) As regards the choice of specific antihypertensive agents,
some guidance can be obtained by analysis of various antihypertensive trials. In general, the degree of blood pressure reduction obtained is more important than which agents are used. Moreover, because therapy requires use of multiple antihypertensive medications at the outset, the preferred initial drug is a moot point. Nevertheless angiotensin-converting enzyme inhibitors (ACE-I) have generally been recommended as preferred initial drugs. There are persuasive data from the Heart Outcomes Prevention Evaluation (HOPE) study in support of the use of ACE-I.\(^4\) Approximately 3500 patients with diabetes with at least 1 additional classic CV risk factor were randomized to either placebo or ramipril in the study. Patients with proteinuria, congestive heart failure, recent MI, or stroke were excluded (as these are established indications for ACE-I). The combined outcome of MI, stroke, and CV deaths was significantly lower in the ramipril-treated group.

Although ACE-I remain the cornerstone of therapy for patients with type 1 diabetes and nephropathy, the RENAAL (Reduction of End Points in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial) studies support initial therapy with angiotensin receptor blockers (ARBs) in type 2 diabetes. The RENAAL study showed that losartan improves renal outcomes in patients with type 2 diabetes and nephropathy more than that attributable to blood pressure control alone. The renoprotective effect of losartan corresponded to an average delay of 2 years in the need for dialysis or kidney transplantation. CV outcomes were secondary end points in the RENAAL and IDNT trials, and with the exception of heart failure for losartan, no benefits on CV outcomes were statistically significant. In contrast, the HOPE trial showed that ACE-I, specifically ramipril, had the greatest evidence for prevention of CV outcomes in patients with renal insufficiency, regardless of diabetic status. Because evidence has shown that patients with increased serum creatinine level (\(>1.4 \text{ mg/dL}\)) are just as likely to die from CV disease as they are to reach end-stage renal disease, it is unclear which should be the focus for treatment. Using a strictly evidence-based approach, this question can only be answered by yet another large, long, randomized controlled trial. Given the similarity of actions between ARB and ACE, it is likely there is considerable overlap of both benefits and side effects between the two, although ARB may have a lower incidence of cough and hyperkalemia. Nevertheless, ARBs represent the only evidence-based treatment strategy for patients with type 2 diabetes mellitus and proteinuria, and have been recommended as initial treatment of choice by the National Kidney Foundation.\(^4\) To conclude, pharmacologic therapy to block the renin-angiotensin-system should be mandatory in patients with diabetic nephropathy (which includes patients with microalbuminuria). In the absence of evidence-based data, the selection of the

![Fig. 13. ADVANCE: effect of therapeutic strategies on combined macro-/microvascular events. (Data from Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829.)](image-url)
appropriate antihypertensive agent should be tailored to the needs of the patient with careful consideration of both medical and economic factors.

β-Blockers are recommended and provide cardioprotection in patients with established CHD, and therefore when additional therapy is needed, β-blockers should be considered in appropriate patients. The role of calcium channel blocker therapy was clarified by the recently published ACCOMPLISH trial. The diabetic subgroup in this study involving 6946 subjects were randomized to treatment with benazepril plus amlodipine or benazepril plus hydrochlorothiazide. A subgroup of 2842 high-risk patients with diabetes (previous CV or stroke events) was further analyzed. Although the mean blood pressure achieved was similar in both treatment groups, there were clear benefits with the benazepril plus amlodipine combination in CV end points. The difference between the 2 treatment groups showed that contemporary treatment with benazepril and amlodipine was noted to be progressively better in higher-risk groups, that is, individuals with diabetes and high-risk diabetic individuals (Fig. 14).

In summary, reduction of increased blood pressure to the target blood pressure should be the primary goal. This point is well demonstrated in the UKPDS study, which showed that in the group with aggressive blood pressure control with either captopril or atenolol, there was no difference in end points, whereas a significant difference was noted between the aggressively treated group and the control group (see Fig. 11). It is appropriate to initiate a specific group of antihypertensive drugs based on compelling indications related to the individual patient. Because most hypertensive patients with diabetes require more than 2 antihypertensive agents, it is prudent to start therapy with at least 2 drugs, usually as a combination product to promptly achieve the target blood pressure and reduce risk of CV events. In general one of those drugs in combination should be a renin-angiotensin-system blocking agent. Based on recent data from the ACCOMPLISH trial, it may be reasonable to consider initial therapy with an ACE-I and dihydropyridine calcium channel blocker especially in the high-risk patient with diabetes. Assimilating the findings of the ACCORD and ADVANCE trials, it is likely that JNC 8 will give specific recommendations for the management of blood pressure in the patient with diabetes.

**Hyperglycemia**

A causal relationship between hyperglycemia and microvascular disease is well established. Studies have also documented benefit of glycemic control by delaying or preventing manifestations of microvascular disease. However, the relationship between hyperglycemia and macrovascular disease has been a subject of constant debate. The largest study

---

**Fig. 14.** Time to first events in major patient subgroups: ACCOMPLISH trial. (Adapted from Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56:77–85; with permission.)
addressing this issue is the UKPDS. It was a study designed to answer the question whether intensive control of glucose compared with conventional treatment in newly diagnosed type 2 diabetics lowers the risk of complications. After a mean follow-up of more than 10 years of approximately 2500 patients in each group, intensive therapy showed a 12% reduction in any diabetes-related end point and a significant reduction in the microvascular end points (25% reduction; \( P = .0099 \)). A 16% reduction in MI (\( P = .052 \)) and nonsignificant reduction in diabetes-related and all-cause mortality was noted in the intensively treated group. Thus, although the value of tight glycemic control for prevention of microvascular disease is undisputable, the UKPDS does not strongly suggest a similar benefit in controlling macrovascular disease.

The EPIC-Norfolk study found a continuous relationship between all-cause mortality and glycated hemoglobin, even for values in the nondiabetic range. In this European study, 4662 men aged 45 to 79 years who had had glycated hemoglobin measured at the baseline survey in 1995 to 1997 were followed up to December 1999. The main outcome measures were mortality from all causes, CV disease, ischemic heart disease, and other causes. Men with known diabetes had increased mortality from all causes, CV disease, and ischemic disease (relative risks 2.2, 3.3, and 4.2, respectively, \( P < .001 \) independent of age and other risk factors) compared with men without known diabetes. The increased risk of death among men with diabetes was largely explained by the HbA\(_{1c}\) concentration. HbA\(_{1c}\) was continuously related to subsequent all-cause, CV, and ischemic heart disease mortality throughout the population distribution, with lowest rates in those with HbA\(_{1c}\) concentrations less than 5%. An increase of 1% in HbA\(_{1c}\) was associated with a 28% increase in risk of death independent of age, blood pressure, serum cholesterol level, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), and cigarette smoking habit; this effect remained after men with known diabetes, an HbA\(_{1c}\) concentration of 7% or more, or history of MI or stroke were excluded. These data argue in favor of the 16% risk reduction for MI in UKPDS being a significant difference.

Postprandial hyperglycemia has also been identified as a potential risk factor for CV disease. The DECODE study was undertaken on the initiative of the European Diabetes Epidemiology Study Group in 1997. Baseline data on glucose concentrations at fasting and 2 hours after the 75-g oral glucose tolerance test from 13 prospective European cohort studies, which included 18,048 men and 7316 women aged 30 years or older were collected. After a mean follow-up period of 7.3 years, mortality increased with increasing 2-hour glucose within each fasting glucose classification. However, for 2-hour glucose classifications of impaired glucose tolerance and diabetes, there was no trend for increasing fasting glucose concentrations, which would suggest that fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia. However, there are no universally accepted guidelines for therapy. The American College of Endocrinology recommends a 2-hour postprandial glucose level of less than 140 mg/dL.

The threshold to which glycemic control needs to be corrected has probably been adequately answered by the recently published data from the ACCORD trial. The goal of the trial was to evaluate intensive glycemic control through currently available means (ie, glycated hemoglobin [HbA\(_{1c}\) <6%], compared with standard glycemic control (ie, HbA\(_{1c}\) 7.0–7.9%) among patients with type 2 diabetes mellitus with known CV disease or with additional risk factors for CV disease. At 1 year, HbA\(_{1c}\) was 6.4% versus 7.5%, respectively. The glycemic arm of the trial was stopped prematurely because of excess deaths reported in the intensive treatment group. Although there was no identifiable cause for excess death in the intensively treated group in the ACCORD trial, a strategy of lowering HbA\(_{1c}\) to a mean of less than 6.5% may not be advisable. These results were somewhat mirrored by the ADVANCE trial, which is the largest trial on diabetes treatments to date. In this trial, 11,140 patients with type 2 diabetes were randomly assigned to undergo either standard glucose control or intensive glucose control with gliclazide and other agents to achieve an HbA\(_{1c}\) value of 6.5% or less. At the end of 5 years, the mean HbA\(_{1c}\) was 6.5% in the intensive control arm versus 7.3% in the standard therapy arm. The main finding of this study was that gradually implemented intensive glucose control, with a goal of achieving an HbA\(_{1c}\) of 6.5% or less, was associated with a significant reduction in some microvascular complications of diabetes, but not macrovascular complications. Intensive glucose control was also associated with a higher incidence of hospitalizations and severe hypoglycemia. A recent presentation by the ADVANCE group indicated that severe hypoglycemia was associated with significant increased risk of CV and all-cause mortality.

The choice of hypoglycemic therapy should be influenced by consideration of multiple factors including BMI, renal function, comorbidities, financial issues, and patient preferences. In general,
overweight individuals should preferably be initially started on metformin in the absence of contraindications. The thiazolidinediones (TZDs), which form an important therapeutic drug class, are effective in reducing blood sugar. Their hypoglycemic action is mediated by increasing muscle uptake of glucose, thereby decreasing insulin resistance. They also reduce hepatic glucose production. The primary action of these drugs is mediated via activation of the peroxisome proliferator-activated receptor (PPAR)-γ receptor, a nuclear receptor with a regulatory role in differentiation of cells. This receptor is expressed in adipocytes, vascular tissue, and other cell types. These drugs have been shown to improve endothelial function, reduce intraabdominal adipose tissue, improve pancreatic β cell function and exert antiinflammatory actions that may contribute to antiatherosclerotic effects. However, not all these effects may be class effects. Pioglitazone and rosiglitazone are 2 thiazolidinediones that are currently available.

The prospective pioglitazone clinical trial (PROactive) randomized more than 5000 patients with type 2 diabetes and documented CV disease to pioglitazone or placebo as add-on therapy to other hypoglycemic treatment. Among patients with type 2 diabetes, treatment with pioglitazone was not associated with a reduction in the primary composite event compared with placebo at an average follow-up of 3 years. Although pioglitazone was not associated with a reduction in the primary composite event (coronary and peripheral events), it was associated with a reduction in the secondary composite end point of coronary events (death, MI, or stroke). In addition, there was a reduction in the need to add insulin to glucose-lowering regimens. The incidence of heart failure and heart failure hospitalizations was higher in the pioglitazone group compared with placebo. The tendency of pioglitazone for sodium retention may explain the higher heart failure rates in the pioglitazone group.

Meta-analysis of trials using rosiglitazone in the treatment of diabetes show variable results regarding adverse CV outcomes. Concern regarding use of rosiglitazone arose after the meta-analysis by Nissen and colleagues. In this meta-analysis involving 42 trials, a small increase in MI was shown compared with the comparator group (placebo, metformin, sulfonylurea, or insulin). An independent meta-analysis performed by the manufacturers of rosiglitazone (Glaxo-Smith-Kline) showed similar findings. Most studies included in these meta-analyses were not designed to explore CV outcomes, which were not uniformly collected or adjudicated; therefore, MI and other CV events were noted as adverse events. The RECORD study, however, was designed to evaluate the effect of rosiglitazone on CV events and mortality. Of 4447 patients from Europe and Australasia, 2222 people on metformin were assigned to addition of rosiglitazone (1117) or sulfonylurea (1105), and 2225 patients on a sulfonylurea were assigned to addition of rosiglitazone (1103) or metformin (1122). All-cause mortality, CV mortality, and MI were also similar between the rosiglitazone and active control arms. However, these results need to be considered in the context of the small number of events and greater statin use in the rosiglitazone group. The incidence of heart failure was higher as was the risk of bone fractures in the rosiglitazone arm. An updated meta-analysis by Nissen and Wolski published this year, again reported a significantly increased risk of MI (odds ratio 1.28) but not CV mortality. Exclusion of the RECORD trial from the analysis yielded similar results with a higher estimate of the odds ratio for MI. The 2008 ADA and the European Association for the Study of Diabetes (EASD) consensus algorithm recommended against the use of rosiglitazone, because of concern regarding safety and the availability of alternative therapies, including pioglitazone, that do not have the same concerns. The last word on the usefulness of TZDs in the management of hyperglycemia in patients with diabetes continues to be debated and clinicians should make individualized judgment when considering its use for any particular patient.

Recent publication of a 10-year follow-up of intensive glucose control in type 2 diabetes from the UKPDS study cohort has raised the concept of a legacy effect. In the UKPDS study, 4209 patients with newly diagnosed type 2 diabetes were randomized to either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin). In posttrial monitoring, patients returned to community- or hospital-based care with no attempt to maintain their previously randomized therapies. The median follow-up was 17 years, with close to 9 years of posttrial follow-up. Although between-group differences in HbA1c were lost within a year of cessation of assigned treatments, levels of HbA1c continued to decrease in both groups for 5 years reflecting appropriate risk factor management. In the sulfonylurea/insulin group, reduction in risk persisted for microvascular disease and any diabetes-related outcome at 10 years (Fig. 15). In addition, reductions were also noted for diabetes-related death, MI, and death from any cause. Furthermore, in the group treated with metformin, significant risk reductions...
persisted for any diabetes-related outcomes, MI, and death from any cause without any effect on microvascular disease. The persistence and emergence of benefits, despite early loss of within-trial differences in HbA1c levels between the intensive therapy group and the conventional therapy group, has been called the legacy effect.

To summarize, although glycemic control does significantly affect the incidence of microvascular complications the effect on macrovascular CV outcomes is less obvious especially in those with prolonged duration of diabetes or preexisting CV disease. In addition, there seems to be a lower threshold value of glycemic control (HbA1c of 6.5%) under which the risk of therapy may outweigh the benefits. Moreover, the strategy and medications used for glycemic control may have an effect on outcomes. Based on the results of the recent trials as noted earlier, the ACC, American Heart Association (AHA), and ADA issued a consensus statement recommending maintenance of A1c levels at or less than 7% for most people with diabetes and recommending that a comprehensive risk factor reduction should be instituted for CV risk reduction in all patients with diabetes.

**Increased Thrombotic Tendency**

The patient with diabetes has many prothrombotic factors increasing the risk for arterial thrombosis leading to MI or strokes. These include platelet dysfunction, increased fibrinogen levels, increased von Willebrand factor, increased factor VII, increased plasminogen activator inhibitor type-I (PAI-1), and reduced tissue plasminogen activator (TPA) levels. Although various abnormalities in the thrombotic pathway have been described, successful therapeutic interventions have been proved only with antiplatelet therapy, which is discussed briefly in this section.

The multiple biochemical and functional abnormalities in platelet function in type 1 and type 2 diabetes lead to increased platelet aggregability and adhesiveness. The correction of this increased platelet aggregability and adhesiveness with antiplatelet agents such as aspirin should logically reduce CV events in diabetics. Until recently, there were no prospective studies designed for investigating the therapeutic role of aspirin in the diabetic cohort. Evidence available from small diabetic subgroups in studies on the general population was used to guide recommendations about use of aspirin in patients with diabetes. The Primary Prevention Project is one such study that enrolled 1031 diabetic subjects.\(^5\) In this study efficacy of low-dose aspirin (100 mg/d) in primary prevention of CV events was studied in individuals with one or more of the following risk factors: hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI, or being elderly. After a mean follow-up of 3.6 years, there was significantly lower frequency of CV deaths and total CV events in the group treated with aspirin. The US Physicians’ Health Study (USPHS), was a 5 year primary prevention trial on nearly 23,000 healthy men that included 533 men with diabetes. Among the men with diabetes, 4% of those treated with aspirin (325 mg every other day) had an MI versus 10.1% of those who received placebo (relative risk of 0.39). The Antithrombotic Trialists’ (ATT) Collaboration recently published an individual patient-level meta-analysis of the 6 large trials of aspirin for primary prevention in the general population.\(^6\) These trials collectively enrolled more than 95,000 participants, including almost 4000 with diabetes. Overall, the meta-analysis found that aspirin reduced the risk
of vascular events by 12%, with the largest reduction being for nonfatal MI. There was little effect on total stroke or CHD death. Some heterogeneity was noted regarding differences in aspirin’s effects based on sex.

Three of the trials in the meta-analysis focused on the effect of aspirin exclusively among patients with diabetes. The ETDRS trial examined the effect of 650 mg of aspirin daily versus placebo among 3711 patients with type 1 or type 2 diabetes between 18 and 70 years of age with some degree of retinopathy. Patients on aspirin had a lower risk of nonfatal or fatal MI (relative risk 0.85). However, there was a higher but nonsignificant increase in incidence of stroke with aspirin (relative risk 1.18, 99% confidence interval [CI] 0.88–1.58). The POPADAD randomized 1276 adults with type 1 or 2 diabetes more than 40 years old and asymptomatic peripheral vascular disease to aspirin (and/or antioxidant therapy) or placebo. No difference was seen in the 2 composite primary end points (death from CHD or stroke, nonfatal MI or stroke, or amputation above ankle AND death from CHD or stroke). Rates of discontinuation of study medication were high. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study was a randomized, open-label trial of aspirin for primary prevention involving 2539 Japanese patients with type 2 diabetes. After an average follow-up of 4.4 years there was no difference in the primary composite end point of fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease (hazard ratio 0.8, 95% CI 0.58–1.1). The combined secondary end point of coronary and cerebrovascular mortality was significantly different (hazard ratio 0.1, CI 0.01–0.79). However, on a prespecified subgroup analysis, subjects older than 65 years had significantly lower incidence of the primary end point on aspirin.

Thus, none of the trials mentioned provides definitive results. Based on these and other studies, the US Preventive Services Task Force recently recommended encouraging aspirin use in men aged 45 to 79 years and women aged 55 to 79 years, and not encouraging aspirin use in younger adults regardless of the presence or absence of diabetes. Two ongoing studies with combined sample size of more than 15,000 individuals with diabetes will provide additional information on the role of low-dose aspirin for the prevention of CV events. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) is an open-label Italian primary prevention trial comparing aspirin 100 mg daily to no aspirin among adults more than 50 years old with diabetes who are also on simvastatin. The second trial, A Study of Cardiovascular Events in Diabetes (ASCEND), will also examine the effects of 100 mg aspirin daily versus placebo for primary prevention among men and women more than 40 years of age with either type 1 or type 2 diabetes.

To provide guidelines for management, the ADA, AHA, and ACC recently published an expert consensus document recommending low-dose aspirin (75–162 mg/d) as primary prevention for adults with diabetes who are at increased CVD risk (10 year risk of CVD events more than 10%) and are not at increased risk for bleeding (prior gastrointestinal bleeding, peptic ulcer disease, or concurrent use of medication such as nonsteroidal antiinflammatory drugs or warfarin). The accurate determination of CVD risk should be made using clinical tools such as the UKPDS Risk Engine, ARIC CHD Risk Calculator or ADA Risk Assessment Tool (Box 2).

The efficacy of aspirin for secondary prevention of CV events is suggested from a meta-analysis of secondary prevention trials by the Antithrombotic Trialists’ Collaboration (ATC). The ATC meta-analysis included 287 trials with total involvement of 212,000 high-risk patients. In more than 4500 patients with diabetes studied in the ATC, the incidence of vascular events was reduced from 23.5% with control treatment to 19.3% with antiplatelet therapy (P < .01). Although the overall incidence of vascular events in the diabetic subgroup was much higher, the benefit of antiplatelet therapy in the patients with and without diabetes was comparable. In the HOT study, half of the 1501 patients with diabetes mellitus included in each target group were randomly allocated to receive aspirin. The CV event rate was reduced by 15% and MI by 36% compared with placebo. The relative effects of aspirin were similar in nondiabetic and diabetic subjects.

**COMPREHENSIVE CV RISK REDUCTION IN DIABETES MELLITUS**

**Multiple Risk Factor Intervention**

With established diabetes mellitus all modifiable risk factors should be addressed. These include...
hypothesis that individual interventions on single CV risk factors that frequently coexist in the patient with diabetes is essential to provide comprehensive CV risk reduction. This approach is substantiated by results of multiple randomized controlled trials of intensive glycemic control that have failed to show a definite independent link between glycemic control and CV risk reduction. It is thus apparent that to reduce the associated high risk of CV events, the focus of treatment should be on addressing all of the CV risk factors in patients with diabetes, and should not just be confined to glycemic control as the risk of CV events is additive for various risk factors that are frequently present in patients with diabetes.

Intervention should start with dietary advice and advice regarding physical activity. Early initiation of a moderate exercise program may be the best strategy for reducing the risk of later macrovascular complications. Several studies have shown that higher leisure-time physical activity is associated with reduced total and CVD mortality among patients with diabetes or impaired glucose tolerance. The Look AHEAD trial is a multicenter, randomized clinical trial that evaluates the effectiveness of intentional weight loss in reducing CVD events among patients with type 2 diabetes. Although the study is focused on weight loss, its findings are relevant for multilevel intervention effects on CVD risk factors in diabetes. The Look AHEAD investigators conducted an interim analysis to evaluate changes in risk profile at the end of 1 year. Participants assigned to the intensive lifestyle intervention lost an average 8.6% of their initial weight versus 0.7% in the diabetes support and education group (P < .001). A greater proportion of intensive lifestyle intervention participants had reductions in glycemia, hypertension, and lipids, which resulted in decreased requirement of pharmacologic therapy. Dietary advice should include recommendations regarding optimal fat intake. It is recommended that intake of polyunsaturated fat should be limited to 10% of calorie intake, although there is a lack of evidence to support this. Consumption of fish high in omega-3 fatty acids (1–2 servings/wk), reduced the risk of coronary death and total mortality in epidemiologic studies and randomized clinical trials, and this benefit seems to extend to those with diabetes as well. Several cohort studies have also reported an inverse association between whole grain consumption and risk of diabetes and CHD. Moderate alcohol consumption (1–2 drinks or 10–20 g of alcohol per day) shows a benefit on CHD incidence in the general population. This benefit also extends to the diabetic population.

As noted in the preceding discussion in this article, individual interventions on CV risk factors in patients with diabetes give a 15% to 30% risk reduction. The results of these studies have been scrutinized in detail leading to the establishment of treatment guidelines with specific targets regarding glycemic control, blood pressure, and lipid levels (Table 3). Although addressing individual risk factors in the patient with diabetes is a logical extension of the findings from currently available evidence, this has limited potential in achieving the maximal attainable benefit for CV risk reduction. A more appropriate approach would be to address multiple risk factors concurrently with the hope of obtaining a comprehensive risk reduction.

Although such a strategy would require considerable effort on the part of the physician and the patient, available data do suggest a comprehensive risk reduction approach to the management of patients with diabetes is beneficial. The Danish Steno-2 study was the first long-term trial among people with type 2 diabetes to evaluate the effect of an intensified, multi-targeted intervention compared with conventional multifactorial treatment on CVD and its risk factors. At a mean follow-up of 7.8 years, patients receiving the intensive therapy showed a 53% (95% CI 27–76) reduction in risk of CVD. The number needed to treat in the Steno-2 study was 5 (ie, 1 CVD event will be prevented in every 5 patients treated intensively for 7.8 years) (Fig. 16).

The ADDITION study is an ongoing international trial, similar to the Steno-2 protocol. The overall aim of the ADDITION study is to evaluate screening methods for prevalent undiagnosed type 2 diabetes, and to develop and evaluate optimized intensive treatment of diabetes and associated risk factors among people 40 to 69 years of age. The ADDITION investigators recently evaluated changes in CVD risk factor profile at the end of 1 year of follow-up among 79 general practices in the southwestern region of the Netherlands. Overall, the 1-year data indicated that the intensive multilevel intervention resulted in a significant reduction in CVD risk factors without worsening health-related quality of life at the end of the first year of follow-up. The data on incident CVD and mortality from this trial are not yet available.

In summary, there is supportive evidence from trials suggesting a benefit of an intensive multifactorial approach for CVD prevention in diabetes. An
Table 3
Goals for risk factor management in diabetes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal of Therapy</th>
<th>Referenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Complete cessation</td>
<td>ADA, AHA</td>
</tr>
<tr>
<td>Blood pressure (with proteinuria)</td>
<td>&lt;130/80 mm Hg</td>
<td>JNC VII, ADA</td>
</tr>
<tr>
<td></td>
<td>&lt;125/75 mm Hg</td>
<td>JNC VII, ADA</td>
</tr>
<tr>
<td>LDL-C (measured annually)</td>
<td>&lt;70 mg/dL for secondary preventiona</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>For age &gt;40 y</td>
<td>Without CVD but ≥1 risk factor, LDL goal is &lt;100 If LDL is &lt;100 at baseline, statin based on additional risk factors</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>For age &lt;40 y</td>
<td>Without CVD, but estimated to have high risk of CVD, LDL-C goal is &lt;100 mg/dL</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>Triglycerides 200–499 mg/dL</td>
<td>Non–HDL-C &lt;130 mg/dL</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>Triglycerides &gt;500 mg/dL</td>
<td>Fibrate/niacin before LDL lowering</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td></td>
<td>Non-HDL &lt;130 mg/dL Target triglycerides &lt;150 mg/dL</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>HDL-C &lt;40 mg/dL(&lt;50 mg/dL in women)</td>
<td>Increase HDL</td>
<td>ATP III, ADA</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Low-dose aspirin therapy (patients with CHD and other high-risk factors including age &gt;40 y)</td>
<td>ADA, AHA</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hemoglobin A1C &lt;7%</td>
<td>ADA, AHA</td>
</tr>
<tr>
<td>Overweight and obesity (BMI &gt;25 kg/m²)</td>
<td>Lose 5%–7% of body weight</td>
<td>ADA, AHA</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>150 min moderate aerobic exercise or at least 90 min vigorous aerobic exercise/wk (no more than 2 consecutive days without physical activity)</td>
<td>ADA, AHA</td>
</tr>
<tr>
<td>Adverse nutrition</td>
<td>Diets low in fat (&lt;30%) and saturated fat &lt;7%; lower glycemic index (when necessary with caloric restriction); 1.2–2 g sodium/d; alcohol up to 2 drinks/d (1 drink/d for women; 1 drink = 354 mL (12 oz) beer or 120 mL (4 oz) wine, or 44 mL (1.5 oz) distilled spirit)</td>
<td>ADA, AHA, ATP III, OEI, JNC VII</td>
</tr>
</tbody>
</table>

Abbreviations: ATP III, Adult Treatment Panel III; JNC VII, the seventh report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure; OEI, Obesity Education Initiative.

a Per advisory from National Cholesterol Education Program.33
b ADA and AHA,70 JNC 7,71 ATP III,32 for OEI.72
important aim of the multifactorial intervention approach is to actively involve the patient with appropriate education and provide tools for self-care. In addition to dietary advice and weight loss, smoking cessation and regular exercise should be emphasized. Pharmacologic intervention should be targeted to specific goals with an appreciation for potential side effects of such goal-driven therapy, particularly with respect to glycemic therapy. The cost-effectiveness of a multifactorial approach to therapy also deserves attention. In the Steno-2 study, the discounted quality-adjusted life expectancy was 1.66 quality-adjusted life years (QALY) higher for intensive compared with conventional treatment, resulting in an incremental cost-effectiveness of 2538 euros per QALY gained.76

CURRENT STATE OF AFFAIRS AND FUTURE DIRECTIONS

This review clearly documents evidence from large randomized controlled trials, the benefits of comprehensive risk reductions in patients with to lower CV events. So the question arises as to how well this is being incorporated in clinical practice. A recent study reported on the improving trends seen in the management of diabetes mellitus and attendant CV disease based on NHANES data.77 Changes in HbA1c, blood pressure, and total cholesterol were estimated between 1988 and 1994 and between 2005 and 2006 using regression analysis and data from the NHANES. HbA1c fell by 0.68% among US adults with diagnosed diabetes. Among those with diabetes and hypertension, systolic and diastolic blood pressure fell by 5.66 and 8.15 mm Hg, respectively. Among those with diabetes and high cholesterol, total cholesterol fell by 36.41 mg/dL. These improvements were projected to improve life expectancy for persons with newly diagnosed diabetes by a year. Similar estimates were recently published in a study conducted in the United Kingdom.78

Analysis of data with long-term follow-up of large cohorts with diabetes mellitus has raised certain interesting aspects relevant to long-term management. It would seem that early and aggressive goal-directed therapy may potentially have beneficial effects in terms of delaying macrovascular events either by deterring renal failure and or by the legacy effect. In the ADVANCE study, with a protocol involving a multifactorial goal-directed therapy, there is a late separation in the Kaplan-Meier curves for major macrovascular events and death from any cause. Although this was not significant for the duration of follow-up reported in the trial, this might represent the beginning of a long-term risk reduction that might become evident with a longer duration of follow-up. The lessons learned from the extended follow-up of the UKPDS and the Steno-2 study clearly emphasizes the importance of long-term sustained efficacy of comprehensive risk reduction in the patient with diabetes. It would seem that a paradigm of early identification and comprehensive risk reduction with therapy directed toward achieving well-defined targets may prove to be both beneficial and economical in reducing the risk of CV and other complications in patients with diabetes.

Prevention of Diabetes Mellitus as a Therapeutic Strategy

Prevention of type 2 diabetes might be an attainable goal and might have a much larger effect and be more economical given the scale of the problem at present. The prevention of diabetes, especially with therapeutic lifestyle interventions, may indeed be the most attractive strategy because the interventions needed are generally less expensive and would translate to large reductions in health care expenditure with the potential for reduction of macrovascular events. Supportive evidence in favor of diabetes prevention comes from observational studies such as the Nurses’ Health Study, in which 84,941 women were followed up from 1980 to 1996. Almost 90% of the cases of incident diabetes were found in women with obesity, lack of exercise, poor diet, and tobacco abuse.79 The Western Working Group, NCEP, ADA, and other major groups have emphasized the importance of the metabolic syndrome as a potential prediabetic state.13,32,34 Simple measures such as weight
reduction and regular activity can reduce the risk of developing diabetes mellitus and potentially reduce CV disease in this population at risk. During transition from euglycemia to overt diabetes, many patients go through a phase of impaired glucose tolerance or impaired fasting glucose level, defined by an oral glucose tolerance test finding of 140 to 190 mg/dL and a fasting plasma glucose level of 110 to 125 mg/dL, respectively. There is now substantial trial evidence showing that the onset of diabetes can be prevented or at least delayed in this cohort of individuals (Finnish Diabetes Prevention study,80 Diabetes Prevention Program (DPP),81 STOP-NIDDM82).

The DPP trial randomized 3234 obese subjects between the ages of 25 and 85 years at high risk of diabetes (BMI ≥24 kg/m², fasting plasma glucose 96–125 mg/dL and 2-hour plasma glucose between 140 and 199 mg/dL) to intensive lifestyle changes versus metformin (850 mg twice a day) plus information on diet and exercise versus placebo. The study was terminated a year ahead of schedule by the Data and Safety Monitoring Board noting that fewer subjects in the intensive lifestyle group developed diabetes at an average follow-up of 3 years (14% vs 22% and 29% in the metformin and placebo groups, respectively). A 10-year follow-up to the DPP trial, the Diabetes Prevention Program Outcomes, was recently published by Knowler and colleagues.83 In this study, 85% of subjects originally enrolled in DPP joined the long-term follow-up and were offered group-implemented lifestyle intervention. Subjects who were originally assigned to the metformin group continued to receive it. After a 10-year follow-up period, the incidence of diabetes in the lifestyle modification and metformin groups was significantly reduced (34% and 18%, respectively). Based on studies mentioned earlier and other supporting data, the ADA guidelines include the prevention of diabetes in individuals with impaired glucose tolerance or impaired fasting fasting glucose as a goal. The assumption is that prevention of diabetes will also lead to prevention of atherosclerosis, which is yet to be shown from prospective trials.

**SUMMARY**

It is well established that patients with diabetes are at increased risk of CV disease morbidity and mortality. Although the CV risk of individuals with diabetes might be spread over a range depending on concurrent risk factors, the baseline risk attributable to the diabetic state alone is high. The treatment of diabetes has evolved over the years from being focused purely on glycemic control to a more sophisticated approach addressing multiple CV risk factors that tend to coaggregate in these individuals. There are now sufficient evidence-based data to support multifactorial risk intervention with specific targets for goal-directed therapy for both secondary and primary prevention. These interventions have shown survival benefit in addition to prevention of micro- and macrovascular complications. Although in general these studies have shown a 15% to 30% relative risk reduction in CV events, the absolute risk of CV events remains high in the intervention group. Moreover, the incidence of diabetes is reaching epidemic proportions in concert with the obesity epidemic, and morbidity and mortality related to diabetes will continue to have a major effect on the health care status of the world population and health care budget of nations. Interventions directed at prevention of diabetes or at the very least delaying onset of diabetes should be an important aspect in the health care strategy and research in confronting the ongoing epidemic.

**REFERENCES**


84. Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired