

Glycemic Control in the Prevention of Diabetic Complications

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“The goals of appropriate therapy for those with diabetes should include serious effort to achieve levels [of] blood glucose as close to those in the nondiabetic as feasible.”
Elliot P. Joslin, 1935

The relationship between abnormal circulating glucose levels and the development of long-term diabetic complications became apparent soon after the introduction of insulin 70 years ago and the avoidance of early death due to ketoacidosis. Classic observational studies by Pirart described the relationship between increased glycosuria and the ultimate development of diabetic retinopathy, nephropathy, and neuropathy. Nonetheless, it required the findings of randomized, controlled clinical trials to finally and definitively establish the relationship between glucose control and microvascular diabetic complications. With the publication of the Diabetes Control and Complications Trial, the Kumamoto Trial, and the United Kingdom Prospective Diabetes Study, the impact of glycemic control in the development of microvascular complications was confirmed.

Our understanding of the pathophysiology of diabetes—particularly, the dysmetabolic changes seen in type 2 diabetes—includes abnormalities in lipid metabolism, fuel flux, and endothelial function. Diabetes control, therefore, can no longer be viewed exclusively as glucose management. Rather, a more global approach is necessary to minimize risks of both microvascular and macrovascular complications. This article explores data supporting a variety of interventions that have been shown to reduce morbidity and mortality associated with long-standing diabetes mellitus. In addition to acknowledging the relationship between complications and diabetic metabolic abnormalities, this article presents a health economics perspective by examining the cost-effectiveness and health utility of these interventions.

GLYCEMIC CONTROL

Although Elliot Joslin hypothesized the relationship between glucose and diabetic complications almost 70 years ago, many scientists of the mid-20th century believed diabetic complications to be an independently inherited abnormality of the blood vessel and basement membrane. In the early 1980s, the National Institutes of Health initiated the

Diabetes Control and Complications Trial (DCCT) to directly address 2 questions: (a) Could intensive insulin therapy of individuals with type 1 diabetes achieve a statistically significant lowering of hemoglobin A_{1c} (HbA_{1c}) levels as compared with conventional therapy? and (b) Could such a reduction in HbA_{1c} levels delay the onset or slow the progression of diabetic microvascular complications?

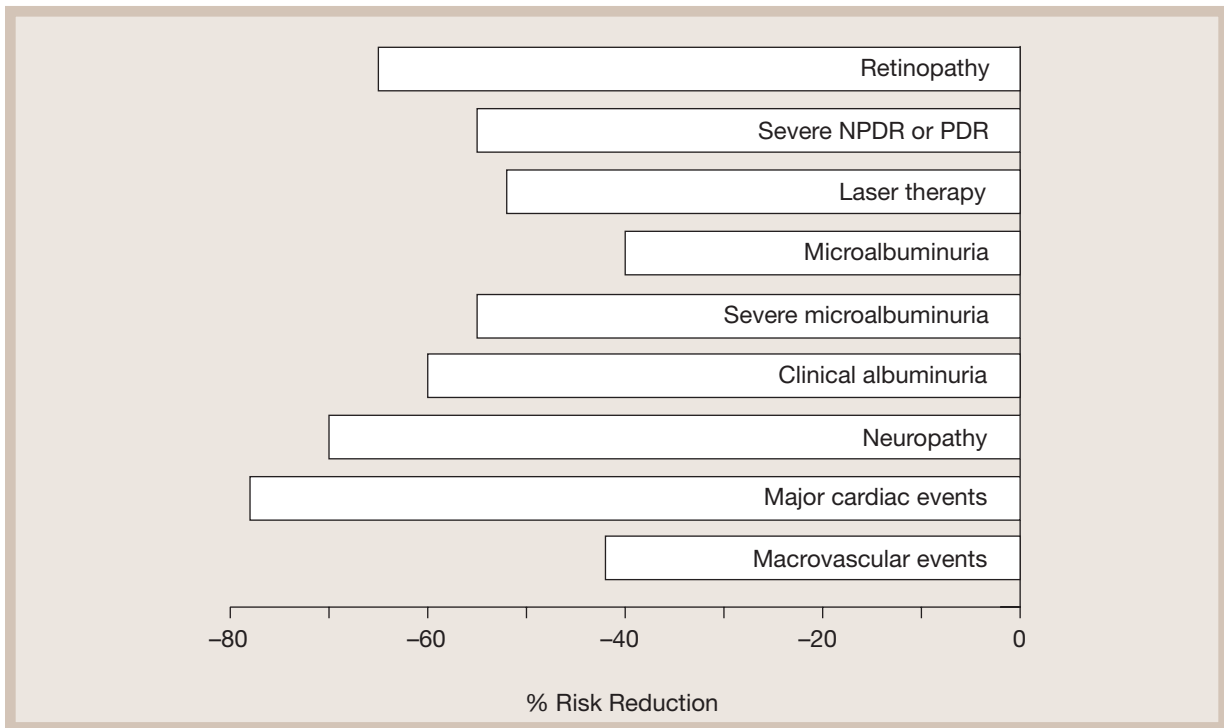


Figure 1. Diabetes Control and Complications Trial risk reductions. NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy. This figure was derived from The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–986.

More than 1400 individuals with type 1 diabetes were entered into the DCCT and stratified on the basis of microvascular disease at study entry, which established a primary and a secondary prevention cohort. Both cohorts were randomized to receive either conventional or intensive insulin therapy. The conventional therapy group was treated with 1 or 2 injections of insulin per day with optional home blood glucose monitoring. Patients were followed by their personal physician with the goal of avoiding symptoms of either hyperglycemia or hypoglycemia. The intensively treated group received either 3 or 4 injections of insulin daily (or use of an insulin pump) with mandatory self-monitoring of blood glucose and frequent contact with study-supported diabetes nurse educators for adjustment of insulin doses in an effort to reduce fasting and preprandial glucose to levels <120 mg/dL and postprandial glucose to levels <180 mg/dL.

Although designed to run for 10 years, the study was stopped prematurely by the Data Safety

Monitoring Board because of a profound difference in both primary and secondary outcomes between the intensively and conventionally treated groups (**Figure 1**). Within the primary prevention group (those with no evidence of microvascular disease at trial entry), development of diabetic retinopathy, defined as a sustained 3-step deterioration in eye findings, was reduced 76% by intensive therapy. Nephropathy, defined as an albumin excretion rate >40 mg/24 hours, was reduced 35%, and clinical neuropathy was reduced 70%. In the secondary prevention cohort (those with evidence of microvascular disease at trial entry), progression of retinopathy was reduced 54%, with a 46% reduction in proliferative and severe nonproliferative diabetic retinopathy. Laser therapy was reduced 54%. Fixed proteinuria >300 mg/24 hours was reduced 56%, and clinical neuropathy was reduced 58%. Clearly there was a trend toward a reduction in macrovascular disease; however, overall event rates were too low in this young patient population to provide statistical power.

Although providing definitive evidence of the relationship between glycemic control and complications in type 1 diabetes, the DCCT left open the question of this relationship in type 2 diabetes. The Kumamoto study followed the DCCT study design and applied it to a population of thin Japanese patients with type 2 diabetes. Investigators showed that intensive insulin therapy reduced the HbA_{1c} level to a mean of 7.1% (as compared with 9.3% in the standard treatment group) and sustained it for a period of 6 years. Reductions in microvascular diabetic complications mirrored the findings of the DCCT almost exactly. Many criticized this study, however, because the characteristics of the patient population were so unlike those typically found in the Western world. These patients were thin and without significant insulin resistance, leading critics to question whether the results could be generalized to the population of type 2 diabetic patients at large.

The United Kingdom Prospective Diabetes Study (UKPDS) was initiated in 1976 to address the question, can an intensive glucose control policy reduce the risk of diabetes complications? Newly diagnosed patients with type 2 diabetes were entered into a diet therapy phase prior to randomization. Those individuals who remained asymptomatic with fasting plasma glucose (FPG) levels between 110 and 270 mg/dL entered the primary randomization. More than 2400 individuals entered into a nonobese cohort, and another 1700 individuals entered a separate randomization for obese individuals. More than 1100 individuals comprised the conventional arm of the study in which initial therapy with diet alone was intended to maintain near-normal body weight, keep the patient asymptomatic from the standpoint of hyperglycemia, and ensure FPG levels <270 mg/dL. When symptoms of hyperglycemia developed or FPG exceeded this threshold, pharmacologic therapy was initiated.

Intensive sulfonylurea, metformin, or insulin therapy was provided to ~2800 obese and nonobese individuals with a goal of reaching FPG levels <110 mg/dL. A step-therapy approach was initiated because participants developed symptomatic hyperglycemia despite initial randomization to either sulfonylurea, metformin, or insulin. These investigators showed an initial reduction in HbA_{1c} levels

KEY POINT

The UKPDS confirms the suggestion of the Kumamoto study that microvascular complications of diabetes are preventable in patients with type 2 diabetes as was demonstrated for type 1 diabetics in the DCCT.

from 7% to 6.2% in the intensively treated group but a slow deterioration in glycemic control in both the intensively and conventionally treated groups over time. Despite the deterioration from 6.2% at year 1 to 7.9% at year 15, the intensively treated group maintained a 0.9% lower HbA_{1c} level at virtually all points in time compared with the conventionally treated group. Also, despite deteriorating glycemic control, the intensively treated group noted a 12% overall reduction in diabetes-related endpoints, with a 25% reduction in specific microvascular disease endpoints (**Table I**). In particular, retinopathy was reduced by 21% and albuminuria was reduced by 33% at 12 years of follow-up. Macrovascular endpoints were a bit more problematic, with no difference in stroke shown between the groups and a reduction of 16% in myocardial infarction (MI) among the intensively treated group not achieving statistical significance. The primary randomization demonstrated no differences in complication rates between those individuals randomized either to sulfonylureas or insulin therapy.

Within the obese cohort of 1700 individuals, 340 were randomized to metformin therapy. In this subgroup analysis, metformin therapy utilized in an intensive fashion in overweight individuals resulted in a 32% reduction in any diabetes-related endpoint, a 42% reduction in diabetes-related deaths, and a 39% reduction in MI. The specific advantages of metformin therapy have been strongly debated. It is important to understand that this was a post hoc subgroup analysis with extensive crossover between treatment groups; thus, very few subjects randomized to metformin were exclusively

TABLE I.

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY
ON GLYCEMIC CONTROL

<i>Complication</i>	<i>Relative Risk Reduction (%)</i>
Diabetes-related endpoints	12
Microvascular endpoints	25
Retinal photocoagulation	29
Retinopathy at 12 years	21
Microalbuminuria at 12 years	33
Myocardial infarction	16 (NS)
Cataract extraction	24

NS = not significant. Adapted with permission from United Kingdom Prospective Diabetes Study Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998;352:837–853.

treated with metformin. For example, the interesting observation that individuals who failed to respond to metformin therapy and received combination therapy with metformin and a sulfonylurea actually had a higher incidence of MI was believed to be due to chance alone. However, this points out the vagaries of post hoc subgroup analysis and further limits the interpretation of the UKPDS. Nonetheless, the UKPDS confirms the suggestion of the Kumamoto study that microvascular complications of diabetes are equally preventable in patients with type 2 diabetes as was demonstrated for type 1 diabetics in the DCCT.

With these data in hand, it is now the obligation of the health care system to determine whether the described interventions in both type 1 diabetes and type 2 diabetes can be applied in a cost-effective manner to the population as a whole. Cost-effectiveness analyses of both the DCCT and the UKPDS findings demonstrate the societal benefits of such interventions. In the UKPDS, intensive diabetes therapies were ~\$1000 per person/year more expensive than conventional intervention, but the resulting reduction in the cost of treating complications resulted in a net decrease in expense of \$385 per person/year for the intensively treated group. Ultimately, the cost per event-free year of intensive blood glucose control in persons with type 2 diabetes was \$1714.

This is consistent with computer modeling

KEY POINT

From both an individual and a societal perspective, glycemic control is a cost-effective intervention for minimizing microvascular complications in diabetes.

undertaken by Eastman et al of the cost-effectiveness of intensive therapy of type 2 diabetes. The computer projections showed that comprehensive care in an individual with type 2 diabetes is more expensive than standard care by ~\$20,000 per person over a lifetime. When projected prevention of blindness, renal failure, and amputations is applied to a formula to obtain a health utility, more than 1,000,000 quality-adjusted life years (QALY) are gained by the introduction of intensive therapy. When one now takes the cost of implementing such an intensive therapy for the population at large with type 2 diabetes and divides it by the expected reduction in complications in improvement and QALY, a figure of ~\$22,000 per QALY gained is obtained (**Figure 2**). This is believed to be extremely cost-efficient and comparable with the cost-effectiveness of treating patients with diastolic blood pressures (DBPs) >105 mm Hg. Furthermore, the cost-effectiveness of intensive management of type 2 diabetes is greatest for those

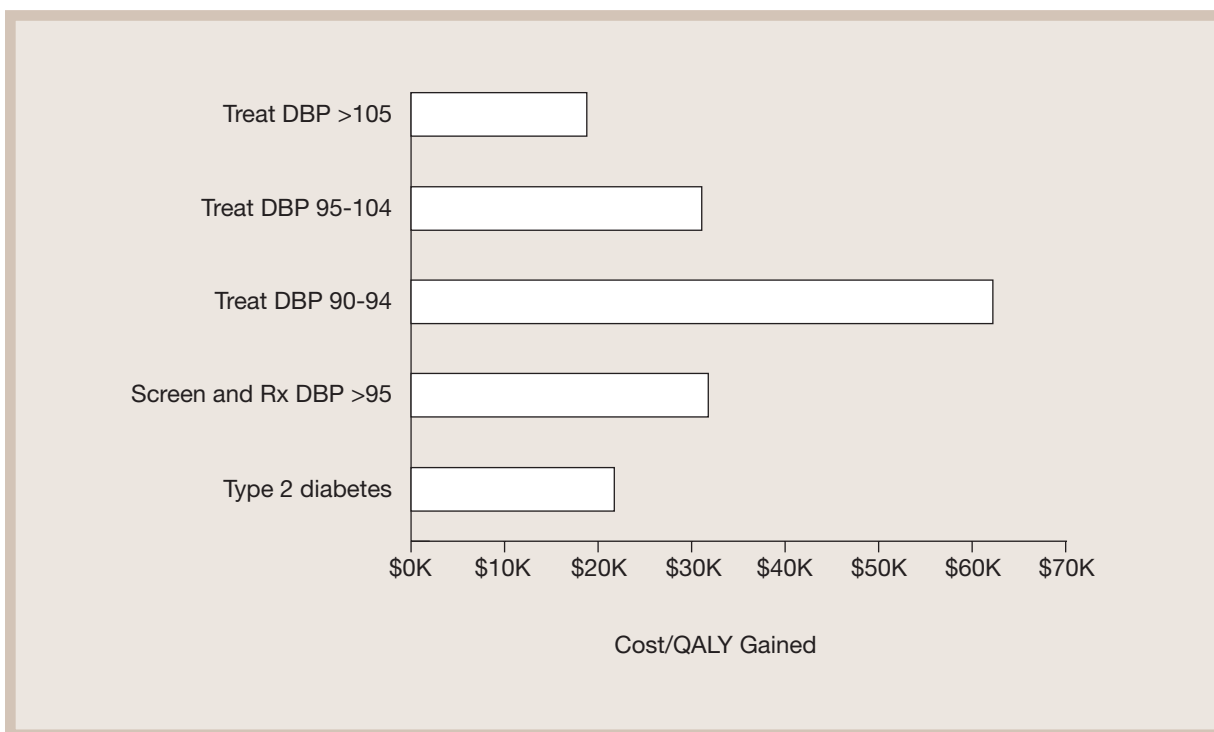


Figure 2. Cost-effectiveness of treating chronic disease. Hypertension and cholesterol treatment analysis in 1994 dollars. Type 2 diabetes this analysis, assuming 100% effectiveness of treatment yielding hemoglobin A_{1c} 7.2%. Discount rate 5% year. DBP = diastolic blood pressure; Rx = treatment; QALY = quality-adjusted life years. From Stason WB. Costs and benefits of risk factor reduction for coronary heart disease: insight from screening and treatment of serum cholesterol. *Am Heart J.* 1994;119:18–24.

patients with higher HbA_{1c} levels. In other words, it is more cost-effective to intensify therapy for a patient with an HbA_{1c} level of 11% than one with an HbA_{1c} level of 8%.

The practical applications of such interventions have been noted by several health care institutions. Gilmer et al examined the costs related to HbA_{1c} levels in a health management organization in California. A 36% increase in charges for individuals with uncomplicated diabetes was noted as the HbA_{1c} levels rose from 6% to 10%. For those individuals with diabetes complicated by hypertension and cardiovascular (CV) disease, the baseline charges were 6 times higher, but the increment from an HbA_{1c} level of 6% to an HbA_{1c} level of 10% was still 28%. Perhaps more important, this group demonstrated a significant cost differential over only a 3-year period with a 1% reduction in HbA_{1c} levels. Cost savings of \$1200 were noted in patients with uncomplicated diabetes by a reduction in HbA_{1c} levels from 10% to 9%, which rose to

>\$4000 for the same HbA_{1c} level reduction in those individuals whose diabetes was complicated by hypertension and CV disease.

The practical applicability of intensive management of type 2 diabetes was demonstrated over time by Meldrum et al. Reduction in HbA_{1c} levels from 8.7% to 7.5% was achieved over a 3-year period in a group practice setting. Total patient costs were not significantly different between year 1 and year 3. However, a redistribution of those costs was noted with a 42% increase in outpatient pharmacy costs, a 16% increase in outpatient visit costs, but a 47% reduction in hospital professional costs.

In summary, the relationship between diabetic microvascular disease and glycemic control has been established in populations with either type 1 diabetes or type 2 diabetes. How one achieves the glycemic control has not been shown to make a substantial difference in the development of these microvascular complications. These clinical interventions are practical and applicable to a broad range

of patients within society and can be implemented by our current health care providers. In addition, the moderate excess costs of initiation of such intensive therapy are rapidly offset by reductions in hospitalizations and emergency room visits and the long-term reduction in complication rates. From both an individual and a societal perspective, glycemic control is a cost-effective intervention for minimizing microvascular complications in diabetes.

The absence of overwhelmingly convincing data on the reduction of macrovascular disease in diabetes has raised the prospect that diabetes control is no longer solely limited to glucose control. Management of those abnormalities associated with diabetic dysmetabolism would seem particularly important in avoiding macrovascular complications. Thus, we now need to examine the effects of blood pressure (BP) control and lipid management as part of the overall scheme of diabetes control.

BLOOD PRESSURE CONTROL

Hypertension has long been noted as a comorbid finding in both type 1 and type 2 diabetes. Epidemiologic studies have demonstrated that individuals with diabetes complicated by hypertension have a far greater probability of developing both microvascular complications such as retinopathy and nephropathy and macrovascular complications such as stroke and MI. Even at clinical states beyond which glycemic control appears to offer no reduction in the progression of complications, it has been demonstrated that institution of BP management significantly slows the development of end-stage renal disease. BP lowering, in general, and angiotensin-converting enzyme (ACE) inhibitor therapy, in particular, slow both the development of microalbuminuria and the progression from fixed proteinuria to end-stage renal disease, dialysis, and death.

In individuals with advanced type 1 diabetes complicated by fixed proteinuria >500 mg/day, captopril therapy reduced the occurrence of the primary outcome (doubling of serum creatinine) but, more importantly, reduced the progression to end-stage renal disease requiring renal replacement therapy and overall mortality. These effects were noted despite equivalent BP control in the control group with a non-ACE inhibitor. Smaller studies

have suggested a similar ACE inhibitor-mediated reduction in the progression from normal proteinuria to microalbuminuria or from microalbuminuria to fixed proteinuria in patients with type 2 diabetes. Recent studies have also suggested that the angiotensin-receptor blockers may have similar beneficial effects independent of BP control. However, only limited studies have directly compared ACE inhibitors with angiotensin-receptor blockers in their capacity to reduce progression of diabetic nephropathy.

Although hypertension is a well-established risk factor for CV disease in the nondiabetic population, the impact on CV event rates of progressive increases in systolic blood pressure (SBP) is twice

KEY POINT

BP control appears to independently affect the progression of both microvascular and macrovascular complications of diabetes.

as great in those with diabetes. The UKPDS introduced a BP control study comparing ACE inhibitors and β -blockers in both intensive and conventional control. No apparent differences in diabetic outcomes were noted between the ACE inhibitor and β -blocker groups, although more side effects were noted with β -blockers. Although the levels of BP achieved in the study were considerably higher than we would currently accept (154/87 mm Hg versus 144/82 mm Hg), the intensive therapy significantly reduced the occurrence of microvascular disease, stroke, heart failure, and diabetes-related deaths. Thus, BP control appears to independently affect the progression of both microvascular and macrovascular complications of diabetes.

How low to target the BP remains problematic. The UKPDS failed to achieve the goal of 130/85 mm Hg recommended by the Sixth Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JNC-VI). Support for these lower thresholds in diabetes comes from the Hypertension Optimal Treatment (HOT) trial and the Systolic

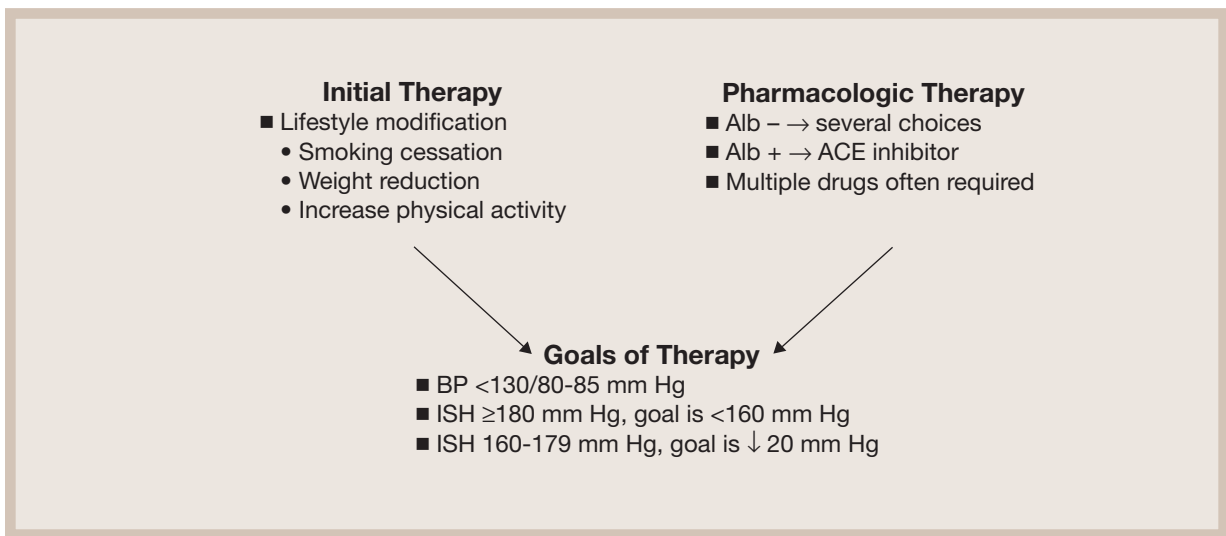


Figure 3. American Diabetes Association guidelines for the treatment of high blood pressure. Alb = albumin; ACE = angiotensin-converting enzyme; BP = blood pressure; ISH = isolated systolic hypertension. From American Diabetes Association. *Standards of medical care for patients with diabetes mellitus.* Diabetes Care. 2000;23(suppl 1):S32–S42.

Hypertension in Europe (Syst-Eur) trial. In the HOT trial, patients with and without diabetes were randomized to target DBP goals of ≤80 mm Hg, ≤85 mm Hg, and <90 mm Hg. CV event rates were reduced by 25% at DBP of ≤85 mm Hg and 48% at a DBP of ≤80 mm Hg as compared with DBPs of <90 mm Hg in the diabetic group only. No effect was seen in the nondiabetic group. Active therapy in the Syst-Eur trial similarly reduced CV event rates by 62% in the diabetic group but only by 25% in the nondiabetic cohort.

The choice of primary antihypertensive therapy has also remained controversial. The UKPDS demonstrated no difference in CV event rates between patients aggressively treated with ACE inhibitors as compared with β-blockers. Others, however, have shown improved CV outcome with ACE inhibitor therapy. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial compared an ACE inhibitor (enalapril) with a dihydropyridine calcium channel blocker (nisoldipine). The study was stopped prematurely because of a marked excess of MIs and CV deaths in the calcium channel blocker group. Compared with enalapril, nisoldipine resulted in a fivefold increase in MI and a doubling of CV mortality. The specific benefits of ACE inhibitor therapy are further supported by the Heart

Outcomes Prevention Evaluation (HOPE) study findings. With only a small difference in BP (2.45 mm Hg systolic/1.0 mm Hg diastolic) between placebo and ramipril therapy, ACE inhibitor therapy reduced MIs by 22%, stroke by 33%, and CV deaths by 37%.

With this evidence base, the American Diabetes Association has recommended therapeutic BP goals of <130/80–85 mm Hg in patients with diabetes (Figure 3). In the presence of microalbu-

KEY POINT

In the presence of microalbuminuria, ACE inhibitors are suggested as the treatment of choice.

minuria, ACE inhibitors are suggested as the treatment of choice; several options are available if no evidence of microalbuminuria is present. Unfortunately, the Third National Health and Nutrition Examination Survey (NHANES III) found that only 11% of diabetic patients have met this goal. Nonetheless, it was demonstrated that these goals are attainable over a 2-year period, with

TABLE II.

DYSLIPIDEMIA OF DIABETES

<i>Increased</i>	<i>Decreased</i>
<ul style="list-style-type: none"> ● Triglycerides ● VLDL cholesterol ● Small, dense LDL-C ● Modified LDL-C (glycated, oxidizable) ● Apolipoprotein B 	<ul style="list-style-type: none"> ● HDL-C ● Apolipoprotein A1

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; VLDL = very low-density lipoprotein.

KEY POINT

The risk of a CV event in an individual with diabetes is equivalent to that of a nondiabetic individual with known CAD.

90% reaching the diastolic goal and 32% the systolic goal with a mean SBP of 133 mm Hg—achieved with just under 3 drugs, which raises concerns of cost, compliance, and drug interactions.

LIPID MANAGEMENT

Lipid changes are an integral part of the metabolic syndrome seen in type 2 diabetes and are frequently seen in association with poorly controlled type 1 diabetes (Table II). Extensive epidemiologic evidence correlates lipid abnormalities with CV event rates, and controlled clinical trials show a reduction in event rates with a reduction in low-density lipoprotein cholesterol (LDL-C) and triglycerides and an increase in high-density lipoprotein cholesterol (HDL-C). Initial trials excluded individuals with diabetes, but more recent studies have incorporated a substantial number of diabetic patients for subgroup analysis, and ongoing studies are now prospectively investigating lipid-lowering strategies in diabetes.

Both of the large secondary prevention trials of CV disease—Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events (CARE)—included large cohorts of individuals

with preexisting or newly diagnosed diabetes (Figure 4). Two seminal observations were made in these studies: statin therapy lowers LDL-C in patients with diabetes as effectively as it does in those without diabetes, and this lipid reduction results in as much or more of a decrease in CV event rates in the diabetic cohort compared with the nondiabetic cohort. In the 4S trial, individuals with and without diabetes entered with a history of coronary artery disease (CAD) and a mean LDL-C of 186 mg/dL and achieved a 37% reduction in LDL-C, an 18% reduction in triglycerides, and an 8% increase in HDL-C. These changes resulted in a 55% decrease in major coronary events, far greater than that seen in the nondiabetic cohort. The CARE study enrolled patients with preexisting

KEY POINT

Two large secondary prevention trials for CV disease have shown that statin therapy lowers LDL-C levels in patients with diabetes as effectively as it does in individuals without diabetes, and this lipid reduction results in as much or more of a decrease in CV event rates in the diabetic cohort compared with the nondiabetic cohort.

CAD and LDL-C levels considerably lower than those found in 4S. Nonetheless, the fall in LDL-C levels was similar between the diabetic and nondia-

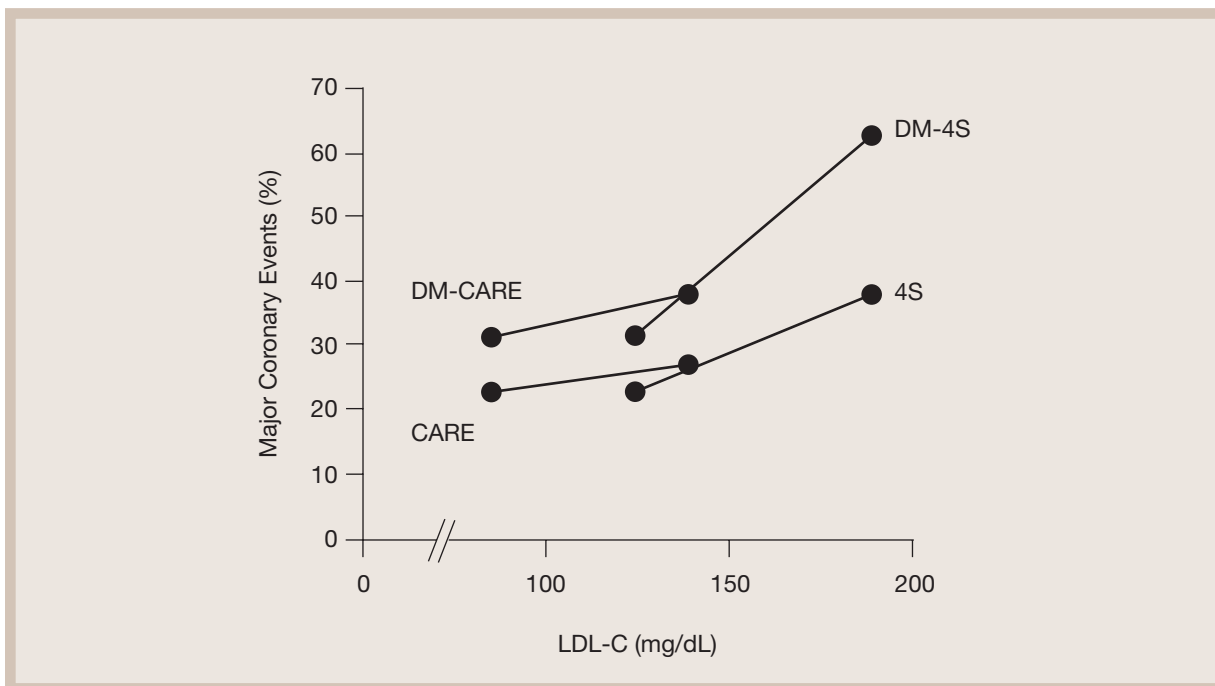


Figure 4. Low-density lipoprotein cholesterol (LDL-C) lowering in diabetic patients. Results of the Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Events (CARE) trial. DM = diabetes mellitus. From Kreisberg RA. Diabetic dyslipidemia. *Am J Cardiol.* 1998;82(12A):67U–73U.

KEY POINT

Clinical trial evidence now exists to support the roles of glycemic control, BP management, and lipid modification—lowering LDL-C and triglyceride levels and increasing HDL-C levels—in reducing diabetic retinopathy, neuropathy, nephropathy, and CV event rates.

betic subgroups, and the reduction in CV event rates was proportionately greater in the diabetic subgroup.

As the LDL-C level comes closer to the normal range, the importance of low HDL-C as a CV risk factor rises. The Veterans Affairs HDL Intervention Trial (VA-HIT) enrolled 627 diabetic participants with entry level LDL-C of 111 mg/dL and HDL-C of 32 mg/dL. Active therapy with gemfibrozil had no effect on LDL-C but dropped

triglycerides by 24% and increased HDL-C by 7.5%. A 24% reduction in the CV event rate was noted, with no difference between the diabetic and nondiabetic groups.

The risk of a CV event in an individual with diabetes is equivalent to that of a nondiabetic individual with known CAD. In effect, all individuals with diabetes are treated according to protocols for secondary prevention of a CV event. This has recently been recognized by the National Cholesterol Education Program Adult Treatment Panel III (ATP III), which designated diabetes as a coronary heart disease equivalent. In addition, the ATP III set thresholds for treatment initiation and therapeutic goals in persons with diabetes that are identical to those for persons with known coronary disease. These include initiation of medical nutrition therapy for persons with LDL-C levels >100 mg/dL and pharmacologic therapy for persons with LDL-C levels >130 mg/dL, with the goal of reaching an LDL-C level of <100 mg/dL.

The cost-effectiveness of lipid intervention has been clearly demonstrated with actual cost savings

TABLE III.

MEANS OF
DIABETES CONTROL

- Glycemic control
–HbA_{1c} ideally <7%
- Blood pressure control
–<130/80 mm Hg
- Lipid control
–LDL-C <100 mg/dL
–Triglycerides <200 mg/dL
–HDL-C >45 mg/dL
- Smoking cessation
- Aspirin

HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

occurring when applied to the diabetic population. In the 4S trial, the reduction in hospitalizations and length of stay in those hospitalizations that did occur resulted in an average cost savings of \$1800 despite the cost of drug therapy for those diabetic individuals in the active therapy arm. Nonetheless, only 42% of diabetic patients surveyed in NHANES III had an LDL-C level of <130 mg/dL.

CONCLUSIONS

The definition of diabetes control is expanding to cover not only the glycemic abnormalities inherent in the disease but also the associated changes in lipids and hemodynamics (Table III). Conventional risk-factor-management interventions (eg, aspirin therapy and smoking cessation) are as important, if not more so, for people with diabetes as for the population at large. The diffuse nature of the microvascular and macrovascular complications requires a therapeutic approach to modify all the risk factors historically implicated in their pathophysiology. Clinical trial evidence now exists to support the roles of glycemic control, BP management, and lipid modification—including lowering LDL-C and triglyceride levels and increasing HDL-C levels—in reducing diabetic retinopathy, neuropathy, nephropathy, and CV event rates. National standards are being modified to reflect these data, and the Diabetes Quality Improvement Project has incorporated them into standard mea-

asures for assessing the performance of health care delivery systems across the nation. Available data suggest that although we have much room for improvement, at least we have targets to pursue.

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Dialogue Box

ADVISORY BOARD

Although the DCCT and the UKPDS demonstrated a correlation between good glycemic control and the prevention of microvascular disease, no benefit was demonstrated for macrovascular complications. How might this be explained?

RATNER

In a couple ways. One, it may mean that the threshold for minimizing microvascular complications is higher than the threshold for macrovascular complications. Supporting evidence for this can be found in individuals with impaired glucose tolerance (IGT) who, despite having blood sugars that fail to meet the criteria for diabetes, are still at increased risk for macrovascular disease. What this may be telling us is that we have to shoot for a greater degree of glycemic control. Two, it supports the premise that optimal diabetic care demands a multipronged approach. It's not enough to simply manage the glucose—BP, lipid

management, aspirin use, and other supportive issues are also critically important if the goal is to minimize macrovascular complications.

ADVISORY BOARD

If glycemic control were optimized to normal levels, would diabetics be regarded as coronary heart disease equivalents?

RATNER

Although I think the cardiac risk would drop considerably, I doubt the risk would be eliminated completely. Epidemiologically, individuals with type 2 diabetes have a 2^{1/2}- to 3-fold increased risk of CAD compared with normal populations; patients with IGT have a reduced risk but a risk still 1^{1/2}- to 2-fold higher than baseline. This might be viewed as the incremental difference that glycemia imparts. Other factors must be contributing, and this is probably where the metabolic syndrome plays such a critical role. Independent of its effect on glycemic control, there is evidence



Dialogue Box

that insulin resistance simultaneously impacts pro-coagulant activity, lipids, BP, and the inflammatory response. Once again, this underscores the need for a multipronged approach to diabetes care.

ADVISORY BOARD

For the diabetic patient unable to tolerate an ACE inhibitor, what are the roles of angiotensin-receptor blockers (ARBs) and calcium channel blockers (CCBs)?

RATNER

ARBs are excellent alternatives with 3 studies* just published demonstrating a renoprotective effect in patients with type 2 diabetes. The use of CCBs is a bit more problematic. Although the ABCD Study ended prematurely, it is still unclear whether the results strongly favoring the ACE inhibitor over a CCB stemmed primarily from the former being so much more beneficial or the latter actually having a direct negative effect. Adequate evidence exists that the nondihydropyridines, specifically diltiazem and verapamil, have a beneficial effect at the level of the glomerulus. At this time, it would seem prudent to choose a nondihydropyridine if a physician opts to use a CCB in the setting of diabetes.

ADVISORY BOARD

What are your thoughts regarding the potential additional benefit offered by tissue-specific ACE inhibitors versus circulating plasma ACE inhibitors?

RATNER

The use of tissue ACE inhibition versus circulating plasma ACE inhibition remains controversial. There is good evidence that those ACE inhibitors

that don't have a substantial effect on tissue ACE levels still have a remarkably beneficial impact. On the other hand, the results of the HOPE Study are exciting, particularly for the prevention of diabetes as well as the beneficial impact on CV events; thus, those agents that have tissue ACE activity are clearly of value. At this time, however, we simply don't have the head-to-head comparisons to say that members of one class are better than members of the other class.

ADVISORY BOARD

Do you view insulin as atherogenic?

RATNER

No, I don't. Although both the Paris Prospective Study and the Whitehall Study seem to suggest a link between endogenous insulin levels in nondiabetics and an increased relative risk of coronary disease, it is important to keep in mind that the elevated insulin levels may be simply a marker of insulin resistance. The administration of insulin itself, even in the high doses required in some individuals, clearly does not induce insulin resistance. On the contrary, giving high doses of insulin to reduce high glucose levels actually ameliorates insulin resistance. Thus, I would view the presence of high insulin levels not as the cause of CV disease but rather as a component of the metabolic syndrome, which, in turn, is responsible for increased CV risk. A second premise that argues strongly against insulin being atherogenic is the absolute lack of evidence that high doses of exogenous insulin are more atherogenic than low doses of insulin.

ADVISORY BOARD

If all things were equal, is it preferable to offer the diabetic patient an insulin sensitizer rather than prescribing an exogenous insulin?

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Dialogue Box

RATNER

It depends on the stage of the disease. Diabetes is a disease that evolves. When diabetes is first diagnosed, which is usually many years after its true onset, what you tend to see is severe insulin resistance and relatively normal insulin levels. At this stage, diabetic patients usually aren't hyperinsulinemic—the hyperinsulinemic phase of diabetes is usually present earlier during the stage of IGT and the pure metabolic syndrome. It is during this hyperinsulinemic phase that the most appropriate intervention would be to improve insulin sensitivity. Over time, however, beta cell function deteriorates so that when patients become symptomatically hyperglycemic, insulin levels are either normal or in some patients actually reduced because of beta cell burnout or failure. At this point, we may have little choice but to give either insulin secretagogues or insulin itself. From the UKPDS, we know that neither sulfonylureas nor metformin slow deterioration in beta cell function in type 2 diabetes and there is this inexorable fall in beta cell function over time. Whether the glitazones or the newer agents that will be coming out will help preserve beta cell function is still not known.

ADVISORY BOARD

Is the property of the thiazolidinediones (TZDs) to reduce triglycerides and increase HDL-C a reason to use these drugs earlier in the course of diabetes?

RATNER

Yes, absolutely. I think that from the pathophysiologic standpoint, the time where the use of the TZDs make the most sense is very early in the disease process when patients have IGT or when they just have profound insulin resistance with still normal blood glucoses. Although data sup-

porting such a role are limited and require further study, it should be noted that the Troglitazone in Prevention of Diabetes study in the early part of the Diabetes Prevention Program did suggest benefit in such a setting. The other time that TZDs are most useful is later in the course of the disease, such as the patient who is requiring 200 units of insulin per day. With this patient, the use of a TZD allows you to reduce the insulin dose. With regard to beneficial effects on lipids, it is noteworthy that the HDL-C benefits you see with TZDs are about the same as what you see with fibrates. Their potential value in this regard is obvious when you consider the results of the VA-HIT where an 8% increase in HDL-C had a profound beneficial impact on CV event rates.

ADVISORY BOARD

How important is it to screen a patient for microalbuminuria?

RATNER

I screen for it at least twice a year for a couple reasons. First, the presence of microalbuminuria is the strongest predictor of coronary disease that we know of, even stronger than elevated LDL-C levels, so vigilance for subclinical coronary disease should go up the moment you detect its presence. Second, it gives you a sense of how optimally the patient's BP and glomerular pressure are being controlled. Let's say you have a patient on an ARB or ACE inhibitor and you still find significant microalbuminuria. I would be suspicious if I'm not achieving my BP goals and would order a 24-hour BP monitoring study. These studies are of particular value in the diabetic patient who, unlike nondiabetics, tends to lose diurnal variability in BP. Ordinarily, nondiabetics are referred to as "dippers" because their BP drops overnight. Diabetic patients may not "dip," leading to under-



Dialogue Box

diagnosis and thus undertreatment of hypertension. In the face of persistent microalbuminuria, despite what you think is adequate therapy, be aware that this can be indicative of the need for more aggressive hypertension management.

ADVISORY BOARD

What do you do with patients who already have macroalbuminuria? Do they warrant maximum hypertensive therapy and maximum ACE inhibitor therapy?

RATNER

Yes, I think they do. We know that you can't reverse fixed proteinuria or even slow its progression with glucose control alone. This is where BP management is absolutely critical. Over and beyond BP lowering, the ARBs and the ACE inhibitors appear to have a beneficial renoprotective effect. Although you may not be able to absolutely prevent end-stage renal disease (ESRD), you can slow its progression significantly with optimal use of these agents. Even in those individuals who begin with serum creatinine levels approaching 2 mg/dL and urine protein levels of half or even a gram a day, aggressive ACE inhibition really does slow the progression and potentially can postpone the development of ESRD and the need for dialysis by 3 to 5 years.

ADVISORY BOARD

How low a BP do you aim for?

RATNER

You aim for as low as a patient can tolerate. Recognize that for all patients with chronic renal

disease and proteinuria exceeding 1 gram per day, regardless of whether they are diabetic, JNC-VI guidelines recommend that the BP be optimally reduced to as low as 125/75 mm Hg. Now one of the difficulties that you need to be aware of is that people with diabetes frequently have autonomic neuropathy with orthostatic hypotension. Thus, when you check the BP sitting, that's not good enough—what you really need to do with a patient who has diabetic complications is to check supine and standing BPs. BP control tends to be more problematic in the diabetic patient because if you're addressing both supine and sitting BPs, you're likely to run into problems with orthostasis. Even if you control their BP in the upright position, their overnight BP may still be inadequately controlled, thereby leaving them at increased risk for stroke and MI. This is yet another reason why 24-hour BP monitoring is potentially useful.

ADVISORY BOARD

How do you manage the diabetic patient with well-controlled hypertension in the day but uncontrolled hypertension at night?

RATNER

One approach is to give a higher dose of the antihypertensive agent at bedtime and give a relatively smaller dose in the morning, thereby loading up on the antihypertensives for the period of time the patient is going to be supine. The other approach is to give a short-acting agent, such as hydralazine, just before bedtime. Elevation of the head of the bed may be of value in reducing the nocturnal rise in BP seen in diabetic patients.