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THE BENEFITS AND RISKS OF CONTROLLING BLOOD GLUCOSE LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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A Review of the Evidence and Recommendations American Academy of Family Physicians American Diabetes Association

Diabetes Policy Team: Steven H. Woolf, MD, MPH¹; Mayer B. Davidson, MD²; Sheldon Greenfield, MD³; Hanan S. Bell, PhD⁴; Theodore G. Ganiats, MD⁵; Michael D. Hagen, MD⁶; Valerie Anne Palda, MD, MSc⁷; Robert A. Rizza, MD⁸; Stephen J. Spann, MD⁹

These recommendations are provided only as an assistance for physicians making clinical decisions regarding the care of their patients. As such, they cannot substitute for the individual judgment brought to each clinical situation by the patient's family physician. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication, but they should be used with the clear understanding that continued research may result in new knowledge and recommendations.

¹ Department of Family Medicine, Virginia Commonwealth University

² Clinical Trials Unit, Charles R. Drew University of Medicine and Science, and Department of Medicine, University of California-Los Angeles School of Medicine

³ Department of Medicine, Tufts University School of Medicine

⁴ American Academy of Family Physicians

⁵ Department of Family and Preventive Medicine, University of California San Diego School of Medicine

⁶ Department of Family Practice, University of Kentucky College of Medicine

⁷ Department of Medicine at St. Michael's Hospital and the University of Toronto

⁸ Division Endocrinology, Metabolism and Nutrition, Mayo Medical School

⁹ Department of Family and Community Medicine Baylor College of Medicine

Executive Summary

Epidemiologic evidence demonstrates a continuous and curvilinear relationship between hyperglycemia and the microvascular and neuropathic complications of diabetes, with risk rising progressively as mean blood glucose concentrations increase above normal values. Evidence from randomized controlled trials in patients with type 2 and type 1 diabetes, supported by additional data from observational studies, demonstrates convincingly that lowering glycemia reduces significantly the risk of microvascular and neuropathic complications. Patients with improved glycemic control experience a lower incidence of new (or worsened) retinopathy, nephropathy, and peripheral neuropathy. The evidence that glycemic control affects macrovascular outcomes is less clear. The absolute magnitude of the benefits of glycemic control in patients with type 2 diabetes must be balanced against factors which either may not allow the benefits to be realized (e.g., limited life expectancy, presence of advanced complications, inability or unwillingness to adhere to the regimen) or may place the patient at increased risk (e.g., severe cardiovascular disease, unrecognized hypoglycemia). The absolute magnitude of the benefits of glycemic control depends on a variety of individual clinical variables (e.g., baseline glycosylated hemoglobin level, presence of preexisting microvascular disease). Thus, although the evidence demonstrates that lowering glucose concentration to as close to normal as possible reduces the risk of diabetic complications, patients' individual risk profile and personal preferences should also be considered in setting individual glycemic goals. Pursuing the same blood glucose target in all patients is not appropriate.

INTRODUCTION

Diabetes mellitus is a leading cause of death, illness, and disability in the United States, affecting an estimated 16 million Americans (Centers for Disease Control and Prevention, 1998). Its microvascular and neuropathic complications cause substantial morbidity: Diabetic retinopathy is the leading cause of new cases of blindness among American adults (Klein and Klein, 1995). Diabetic nephropathy is the most common cause of end-stage renal disease (Nelson et al., 1995). Diabetic neuropathy (and vascular disease) produce leg and foot ulcers and their consequences, resulting in half of all lower extremity amputations in the United States (Reiber et al., 1995).

An even greater public health burden arises from the macrovascular complications of diabetes, which substantially increase the risk of death and morbidity from coronary artery disease, stroke, and peripheral vascular disease (Wilson et al., 1991). Because persons with diabetes are at increased risk for cardiovascular disease, the leading cause of death in the United States, the atherogenic consequences of diabetes account for an enormous burden of suffering and rising health care expenditures in the United States. Estimates of the annual direct and indirect costs of diabetes are 44-45 and 46-54 billion dollars, respectively (Javitt and Chiang, 1995; American Diabetes Association, 1998).

About 90-95% of persons with diabetes have type 2 diabetes (Harris, 1995), which is usually diagnosed in adulthood (mean age = 51 years) and is thought to result from a combination of insulin resistance and relative beta-cell failure. Type 1 diabetes usually has its onset during childhood and is characterized by low or absent levels of insulin, autoimmune response leading to beta-cell antibodies as well as antibodies to other components of the islets, and genetic predisposition. Genetic predisposition is even more evident in type 2 diabetes. In both type 1 and type 2 diabetes, the pathogenesis of microvascular (and possibly macrovascular) complications appears to be related to chronic elevations in blood glucose concentrations. The relationship between hyperglycemia and these complications is continuous and curvilinear (as illustrated for retinopathy in Figure 1), with risk rising steadily as mean blood glucose levels increase. We make no distinction between type 1 and type 2 diabetes with respect to microvascular and neuropathic complications; the more overriding factors in predicting the course of the disease appear to be the number of years one has had hyperglycemia and the magnitude of the glucose elevation.

A strong body of evidence suggests that the incidence of microvascular complications can be reduced significantly by therapeutic measures to lower blood glucose to normal or near-normal levels. A seminal study was the Diabetes Control and Complications Trial (DCCT), published in 1993, which showed in a sample of 1441 patients with type 1 diabetes that a program of intensive glycemic control could lower the incidence of retinopathy, nephropathy, and neuropathy by 76%, 44%, and 69%, respectively, over a mean period of 6.5 years (DCCT, 1993). In 1998, a landmark British trial involving 4200 patients with type 2 diabetes (the United Kingdom Prospective Diabetes Study [UKPDS]) reported that the 10-year incidence of microvascular complications was 25% lower in patients who were intensively treated with diet and medications than in those receiving conventional treatment (UKPDS 33, 1998).

The implications of this evidence for blood glucose control are debated, however. Although there is widespread agreement about the importance of lowering markedly elevated blood glucose in patients

with diabetes, the incremental benefit of tight glycemic control (versus less intensive therapy) in patients with type 2 diabetes is modulated by multiple factors. Microvascular complications require a number of years to develop into symptomatic disease. The generally younger patients with type 1 diabetes are more likely to live long enough to experience the benefits of tight glycemic control than are older patients with type 2 disease, who face a shorter life expectancy by virtue of their age and risk of cardiovascular disease. Although several observational studies have shown a correlation between hyperglycemia and mortality, there is only limited evidence that glycemic control can reduce the risk of macrovascular complications. For some type 2 patients, such as those undergoing treatment for other coexistent medical disease, the delayed benefits of glycemic control may be offset by the more immediate inconvenience (blood glucose testing, treatment, office visits), complications (e.g., hypoglycemic episodes), and costs of more intensive treatment and by morbidity and mortality from comorbid conditions.

These tradeoffs are not uniform for all patients with type 2 diabetes. Although the older age of onset that is typical of type 2 diabetes results in a lower average lifetime probability that microvascular complications will develop than is typical of type 1 diabetes, a significant proportion of patients with type 2 diabetes do live long enough to experience significant microvascular disease. The older age of onset reflects a population *average* with a wide age distribution, and thus an important subset of individuals with type 2 diabetes develop the disease earlier in life and are more likely to benefit from glycemic control. Moreover, interventions that enhance life expectancy for persons with diabetes (e.g., smoking cessation, blood pressure and lipid management, use of beta-blockers and angiotensin converting enzyme inhibitors) give greater opportunity for patients to be vulnerable to microvascular complications and to benefit from treatment.

In 1996, the American Academy of Family Physicians established a policy team to review the evidence of benefit and harm from glycemic control in type 2 diabetes. The panel was composed of family physicians, general internists, endocrinologists, and a practice guidelines methodologist, some of whom were appointed by the American Diabetes Association and American College of Physicians. This report summarizes the policy team's recommendations for clinical practice and the review of evidence on which they are based.

REVIEW OF EVIDENCE

METHODOLOGY

The literature review sought published evidence regarding the effects of glycemic control on microvascular and macrovascular complications in type 1 and type 2 diabetes and on the incidence of adverse effects. A manual and computerized search were conducted. In the first phase, relevant articles were identified by examining the reference lists of recent review articles, supplemented by citations noted in the articles retrieved and by suggestions from panel members and experts. In the second phase, a computerized search was conducted to identify articles, especially recent publications, not uncovered by the manual search. The MEDLINE search sought all English-language publications during 1990-1997 involving human subjects and indexed by one of the following MeSH terms: DIABETIC--ANGIOPATHIES, DIABETIC--NEPHROPATHIES, DIABETIC--NEUROPATHIES, DIABETIC--RETINOPATHIES. Two panel members independently reviewed the search results, and all articles selected by either panel member were pulled. A total of 1583 citations were recorded and

798 articles retrieved. Selected articles published after March 1997 were reviewed during the course of the panel's work.

All articles retrieved in the manual search underwent critical appraisal using a review form that identified relevant outcome data and assessed study design and quality. The forms collected information to select studies with relevant data to be transferred to evidence tables. Studies subsequently identified in the computerized search were reviewed by staff, and relevant data were added to the evidence tables.

The panel determined at the outset to search for and assign greater weight to evidence of an effect on health outcomes perceptible to patients rather than to intermediate or surrogate measures that are associated with, or predictive of, such outcomes. For example, evidence that lowering blood glucose is associated with a reduction in retinopathy does not, by itself, describe the extent to which symptoms perceptible to the patient (e.g., visual impairment) are improved. Similarly, the degree to which glycemic control reduces albuminuria does not necessarily parallel a reduction in the incidence of end-stage renal disease. Most trials, however, did not designate these outcomes as the primary endpoints for the studies and therefore lacked the statistical power and duration to either demonstrate or disprove an effect. Accordingly, the lack of evidence of an effect on health outcomes does not prove ineffectiveness.

This report also gives greater weight to evidence from clinical trials than from observational studies of patients with type 2 diabetes, which are summarized but not analyzed in detail. The findings from observational studies (e.g., cross-sectional and cohort studies) reviewed in this report are often inconsistent, due to important differences in patient selection, treatment interventions, outcome measures, length of follow-up, expertise of clinicians, patient compliance, and other design features. Rather than analyzing these differences and examining the extent to which they account for discrepant results, we have chosen instead to focus on evidence from randomized trials, because they provide more direct evidence and are less subject to confounding. However, randomized trials are not without their limitations: they can provide evidence on only selected samples of patients, test interventions under relatively optimal conditions and for limited periods of time, and may use narrow surrogate outcomes. Often they are unable to provide data that are generalizable to community practice. While observational data provide information on a much broader array of interventions and patient populations, controlled trials provide the best venue for testing the efficacy of an intervention in improving outcomes.

The evidence summary that follows is organized around specific microvascular and macrovascular complications and divides the evidence into three categories: observational evidence in type 2 diabetes, clinical trial evidence in type 2 diabetes, and clinical trial evidence in type 1 diabetes. Observational evidence includes cross-sectional, longitudinal, and other descriptive epidemiological studies regarding the strength of the association between glycemic control and health outcomes. *Cross-sectional studies* examine whether patients with elevated blood glucose levels are more likely (at the time of the study) to have evidence of complications from diabetes, and vice versa (whether persons with complications from diabetes are more likely to have elevated blood glucose levels).

Longitudinal cohort studies record blood glucose concentration or glycated hemoglobin levels¹⁰ at baseline (and/or periodically at subsequent checkups) in a group of patients and follow them over time to determine whether baseline or subsequent values predict the likelihood of developing complications. Glycated hemoglobin levels are more stable over time than blood glucose levels (Nathan et al., 1986; Chase et al., 1989; Agardh et al., 1997).

Observational evidence demonstrates the *association*, or correlation, between glycemic control and diabetic complications but provides no direct evidence that lowering blood glucose actually reduces the incidence of complications. There are several reasons why observational data cannot provide this evidence. First, associations do not necessarily prove causality; confounding variables that occur in patients with poor glycemic control may have a more direct role in observed outcomes. Additional elements, such as a dose-response relationship and biological plausibility, must also be demonstrated. Second, reducing exposure to a causal agent (i.e., hyperglycemia) may not have sufficient impact on complication rates to produce a statistically significant change in the incidence or severity of a complication. Third, data from observational studies may be more vulnerable to bias in terms of skewed patient selection, confounding by uneven distribution of risk factors and/or treatments; imprecise definition of interventions, and biased or inaccurate measurement of outcomes.

Evidence that lowering blood glucose concentration achieves a statistically significant effect on health outcomes is therefore best derived from intervention studies (e.g., clinical trials, including randomized controlled trials). Clinical trial evidence compares the incidence of complications among comparable groups of patients who are allocated at the outset to different intensities of glycemic control and followed prospectively over time. Random assignment of patients to the treatment groups reduces the potential influence of confounding variables by distributing them equally among groups. Observed differences in the incidence of microvascular or macrovascular outcomes can be attributed with greater confidence to the intervention under study. The clinical trial evidence is reviewed separately for type 1 and type 2 diabetes. Observational evidence for type 1 diabetes is not reviewed in this report.

The review focuses on the benefits of glycemic control and not on the individual effects of specific glucose-lowering agents (e.g., insulin, sulfonylurea, metformin). Although other interventions not associated with glycemic control, such as laser phototherapy for diabetic retinopathy and angiotensin converting enzyme inhibitors for diabetic renal disease, are particularly effective in preventing the progression of microvascular complications, they are not reviewed here because they do not speak directly to the benefits of glycemic control itself. There is some evidence that improved control of blood pressure may have a synergistic effect on the efficacy of glycemic control (UKPDS 38, 1998).

The panel developed its recommendations directly from the evidence, giving greater weight to evidence from clinical trials than to evidence from observational studies. Letter codes for grading the strength of recommendations (e.g., “A” for recommendations based on clinical trial evidence) were

¹⁰ In this report, the term “glycated hemoglobin” is used to describe a broad category of measures that include total glycosylated hemoglobin, hemoglobin A₁, and hemoglobin A_{1c}. Although these measures are not equivalent, we do not stipulate the specific measure used in each study, referring instead to all measures as “glycated hemoglobin,” because the details are not specified for each study and the general principles apply to each. The normal range for hemoglobin A_{1c}, the most commonly used glycated hemoglobin assay, is generally 4-6%.

not employed so that narrative descriptions could be used to more fully characterize the evidence. The report was reviewed by a panel of outside experts and family physicians, and revisions consistent with the panel methodology were incorporated. The final report was approved in March 1999 by the respective Boards of the American Academy of Family Physicians and the American Diabetes Association.

Overview of clinical trial designs

The essential elements of the study designs of the major randomized controlled trials reviewed in this report are summarized in Table 1. In most studies, patients were randomly allocated to a group that received continuous subcutaneous insulin infusion or multiple insulin injections or to a group that received conventional insulin therapy that was in effect at that time. Most studies were successful in achieving better glycemic control (as measured by mean glycosylated hemoglobin levels) in patient groups receiving continuous or multiple injections. An older trial, the University Group Diabetes Program (UGDP), did not achieve a significant difference in glucose control in some treatment arms and lacked statistical power, thus providing limited insight into the effect of glycemic control on complications. It therefore is not considered further in this review.

The major study in type 2 patients, the UKPDS, employed a complex design (UKPDS 33, 1998; UKPDS 34, 1998). After three months of dietary counseling and clinic visits, approximately 4200 patients were assigned randomly to a conventionally treated group that relied on diet to maintain a fasting plasma glucose of < 15 mmol/L (270 mg/dL) and an intensively treated group that received diet and medications to maintain a FPG of < 6.1 mmol/L (110 mg/dL). The intensively treated group received either sulfonylureas (chlorpropamide, glibenclamide [glyburide], or glipizide) or insulin, determined randomly. Patients were stratified by body weight before randomization. Approximately 1700 subjects who were 20% over ideal body weight were assigned to an imbedded randomized trial that compared the effects of metformin and diet to diet alone.

Over 10 years, the average glycosylated hemoglobin achieved in the conventional and intensively treated groups was 7.9% and 7.0%, respectively. Because the study achieved this significant 11% relative separation in glycosylated hemoglobin levels in these randomly assembled cohorts, we compare outcomes for the conventionally and intensively treated groups as a whole, despite crossovers within groups, because patients were originally assigned to these groups randomly. Embedded trials within the UKPDS (UKPDS 34, 1998; UKPDS 38, 1998), which examined the effects of metformin and of antihypertensive therapy, are not discussed here because they do not speak directly to the efficacy of glycemic control.

Because the UKPDS achieved a more modest absolute separation in glycosylated hemoglobin levels between treatment and control groups than did the DCCT (0.9% versus 1.9%, respectively) and used different outcome measures, direct comparisons of the magnitude of benefit (absolute risk reduction) between the two trials may be subject to misinterpretation. However, the relative risk reductions in the two trials were similar: a 35% reduction was found in the UKPDS and a 45% reduction was reported in the DCCT for every 1% decrease in glycosylated hemoglobin levels.

MICROVASCULAR OUTCOMES

Retinopathy

Retinopathy, along with cataracts and glaucoma, are major causes of decreased visual acuity and blindness in diabetes. Although retinopathy is a major risk factor for developing blindness, not all persons with retinopathy develop visual symptoms. Retinopathy usually progresses through nonproliferative and proliferative stages. *Nonproliferative retinopathy* is characterized by retinal microaneurysms, hemorrhages, hard exudates, cotton-wool spots, intraretinal microvascular abnormalities, and venous beading and reduplication. *Proliferative retinopathy* is characterized by the growth of abnormal blood vessels and fibrous tissue from the optic nerve head or from other areas of the inner retinal surface, which can result in vitreous hemorrhage. Macular edema can occur with either nonproliferative or proliferative retinopathy (Klein and Klein, 1995).

Evidence from Type 2 Diabetes Mellitus

Observational Studies:

Cross-sectional studies demonstrate that persons with type 2 diabetes who have poor glycemic control (increased FPG, glycated hemoglobin, glucose tolerance test results, glycosuria) are more likely to have, at the same time, evidence of diabetic retinopathy (Burditt et al., 1968; Dorf et al., 1976; Klein et al., 1984; Nathan et al., 1986; West et al., 1982; Knuiman et al., 1986; Naliboff and Rosenthal, 1989; UKPDS Group, 1990; Liu et al., 1993; Stolk et al., 1995). Moreover, prospective longitudinal studies show that an elevated FPG concentration (Miki et al., 1969; Howard-Williams et al., 1984; Lee et al., 1992; Chen et al., 1995) or glycated hemoglobin level at baseline (Liu et al., 1993) or over time (Morisaki et al., 1994; Nakagami et al., 1997) significantly increases the chances that type 2 patients will have developed new or worsened retinopathy when they are examined 4-13 years later. Longitudinal studies using broader measures of glycemic control (FPG, frequency of glycosuria, postprandial glucose levels, presence of symptoms of ketosis) generally find a similar correlation (Pirart et al., 1978; Liu et al., 1993; Chen et al., 1995).

The most widely cited longitudinal data for retinopathy in type 2 diabetes comes from a population-based study in which 2366 diabetic patients (996 with type 1 diabetes, 1370 with type 2) in an 11-county region of Wisconsin were identified in 1980, of whom 1878 (891 with type 1 diabetes, 987 with type 2) were followed for 4 years and 1298 (765 with type 1 diabetes, 533 with type 2) for 10 years (Klein et al., 1988, 1994). The results at both points of follow-up for patients diagnosed after age 30 are summarized in Table 2. At the 4-year follow-up, those not taking insulin with a baseline glycated hemoglobin in the third or fourth quartile (glycated hemoglobin $\geq 8.7\%$) were four times more likely to develop retinopathy than those in the first quartile (glycated hemoglobin of 5.4-7.6%) (Klein et al., 1988). Persons with nonproliferative retinopathy and a baseline glycated hemoglobin in the third or fourth quartile were 4-6 times more likely to show signs of progression; the risk of proliferative disease was not significantly higher. After 10 years of follow-up, those not taking insulin who had a baseline glycated hemoglobin in the third or fourth quartile remained three times more likely to have evidence of retinopathy (Klein et al., 1994). Persons with nonproliferative retinopathy and a baseline glycated hemoglobin in the third or fourth quartile were 3-4 times more likely to have progressed; the risk of having developed proliferative disease if the baseline glycated hemoglobin value had been in the fourth quartile was 14 times as great as those whose glycated hemoglobin value had been in the first quartile.

In persons diagnosed after age 30 who were using insulin, a baseline glycated hemoglobin in the second or third quartile (glycated hemoglobin level of 8.9-11.5%) was not predictive of retinopathy, but those with values in the fourth quartile (glycated hemoglobin level of 11.6-17.0%) were twice as likely to have evidence of new or worsened retinopathy at 4- and 10-year follow-up and were three times more likely to have proliferative disease after 10 years (Klein et al., 1988, 1994). Although this study was based on a population-based sample, it may have been vulnerable to selection bias and thus the magnitude of observed risk may not be fully generalizable to the general population.

Evidence from Clinical Trials:

Direct evidence from intervention studies also indicates that *lowering* blood glucose concentrations reduces the incidence of retinopathy in type 2 diabetes. The 110 Japanese patients in the Ohkubo trial included 55 with no retinopathy (primary prevention group) and 55 with nonproliferative retinopathy (secondary prevention group) (Ohkubo et al., 1995). In the primary prevention group, a change in retinopathy of two or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale (Early Treatment Diabetic Retinopathy Study Research Group, 1991) was noted after 6 years in 36% of the patients receiving conventional therapy and in 6% of those receiving multiple injections, an 83% reduction in relative risk ($p=0.04$). In the secondary prevention group, the corresponding relative risk rates were 44% and 17%, respectively ($p=0.05$).

In the much larger UKPDS, which compared outcomes for 1138 conventionally treated and 2729 intensively treated type 2 patients, the aggregate incidence of microvascular complications was reduced by 25%, from 11.4 to 8.6 events per 1000 patient-years ($p = 0.01$) (UKPDS 33, 1988). The authors attributed much of this benefit to reduced incidence of retinopathy. The need for retinal photocoagulation was lowered from 11.0 to 7.9 events per 1000-patient years, a 29% reduction ($p < 0.01$), and within 6 years of follow-up the incidence of a two-step progression on the ETDRS scale (Early Treatment Diabetic Retinopathy Study Research Group, 1991) was lowered from 27.8% to 23% ($p = 0.02$). Cataract extraction was 24% lower ($p = 0.05$) in the intensively treated group. The incidence of decreased visual acuity, blindness, and vitreous hemorrhage did not differ significantly between the groups. The extent to which the latter represents the results of treatment for early complications is not known.

Clinical Trial Evidence from Type 1 Diabetes Mellitus

There is also evidence from intervention studies in type 1 patients that intensive lowering of plasma glucose concentrations can reduce the incidence of future retinopathy. The 1441 patients in the DCCT included 726 without retinopathy (primary prevention group) and 715 with mild-moderate nonproliferative retinopathy (secondary prevention group). In the primary prevention group, after a mean follow-up of 6.5 years, retinopathy (defined as a sustained 3-step change on the ETDRS scale [Early Treatment Diabetic Retinopathy Study Research Group, 1991]) had developed in 91 patients in the conventional treatment group and 23 patients in the intensive therapy group. The incidence of retinopathy was 4.7/100 versus 1.2/100 patient-years, respectively, a 76% reduction in adjusted relative risk ($p<0.002$). Because of their higher absolute risk, most of the cases prevented were in

patients who initially had glycated hemoglobin values of 10% or greater (Diabetes Control and Complications Trial Research Group, 1993).

In the secondary prevention group, the rate of progression of retinopathy with conventional and intensive treatment was 7.8/100 and 3.7/100 patient-years, respectively ($p<0.002$), a 54% reduction in adjusted relative risk (Diabetes Control and Complications Trial Research Group, 1993). Intensive treatment was also associated with a significant reduction in the incidence of severe nonproliferative or proliferative retinopathy (from 2.4/100 to 1.1/100 patient-years, $p<0.04$) and the need for initial laser treatment (from 2.3/100 to 0.9/100 patient-years, $p<0.002$), adjusted relative risk reductions of 47% and 56%, respectively. The reduction in the incidence of macular edema was not statistically significant. The absolute risk of sustained progression (evidence of worsening for at least 6 months) in the secondary prevention cohort was decreased from 5.9 to 2.2/100 patient-years ($p<0.001$), a 65% reduction in adjusted relative risk (Diabetes Control and Complications Trial Research Group, 1995[a]).

The Stockholm trial found a significant difference (mean score of 4.1 versus 3.5 on modified ETDRS scale [Early Treatment Diabetic Retinopathy Study Research Group, 1991]) in the severity of retinopathy after 60 months of follow-up ($p<0.05$) (Reichard et al., 1991). After a median follow-up of 94 months, the prevalence of serious retinopathy was 52% in the conventional group and 27% in the intensive group ($p=0.01$). Moreover, the prevalence of impaired visual acuity was reduced from 35% to 14% ($p=0.02$) (Reichard et al., 1993), possibly the only direct evidence from clinical trials that lowering blood glucose improves symptoms perceptible to patients. Similar results were reported at 10-year follow-up (Reichard et al., 1996). Older, smaller randomized controlled trials confirm an association between multiple versus single injections and the annual incidence of new microaneurysms and hemorrhages (Eschwege et al., 1979; Dahl-Jørgensen et al., 1986).

Not all randomized controlled trials have confirmed that lowering blood glucose reduces the incidence of retinopathy in type 1 diabetic patients. Several trials comparing continuous subcutaneous insulin infusion with multiple or conventional injection regimens have not observed a statistically significant reduction in retinopathy (Dahl-Jørgensen et al., 1986; Kroc Collaborative Study Group, 1988; Beck-Nielsen et al., 1990; Feldt-Rasmussen et al., 1991), but most had sample sizes of less than 50 patients and some had follow-up periods as short as 2 years. The body of evidence supports a positive effect. A 1993 meta-analysis of 16 randomized controlled trials, published before the DCCT, concluded that intensive therapy was associated with a 51% reduction (95% confidence interval for OR=0.28-0.85) in the risk of developing retinopathy and a 56% reduction (95% confidence interval for OR=0.22-0.87) in the risk of progression (Wang et al., 1993).

Peripheral Neuropathy

Evidence from Type 2 Diabetes Mellitus

Observational Studies: Observational studies support a weak association between elevated blood glucose and the development of peripheral neuropathy in persons with type 2 diabetes. In cross-sectional studies, type 2 patients with neuropathy are more likely to have higher plasma glucose or glycated hemoglobin levels than controls (Knuiman et al., 1986; Naliboff and Rosenthal, 1989;

Partanen et al., 1995). Other cross-sectional analyses have reported no significant association between FPG concentrations and vibration thresholds (UKPDS Group, 1990).

Prospective cohort studies have found that elevated blood glucose concentrations predict the future development of abnormal electrophysiologic findings. For example, one study demonstrated through multivariate analysis a statistically significant correlation between baseline FPG concentrations and the probability of developing abnormal vibratory sensation (as measured by a biothesiometer) within 5 years (Hillson et al., 1984[a]). An older study linked glycemic control (as measured by FPG and glycated hemoglobin levels) to improved nerve conduction velocity in the median and tibial nerves but saw no improvement in the peroneal or sural nerves (Graf et al., 1981). A study of 4400 patients found that average blood and urine glucose levels over time were predictive of future neuropathy (Pirart et al., 1978). The WESDR study followed 406 patients for 10 years who did not have a history of neuropathy at baseline. In patients whose diabetes developed after age 30, it found a significant association between baseline glycated hemoglobin values and the onset of diminished tactile and temperature sensation in patients taking insulin (but not in those not taking insulin) (Klein et al., 1996).

Evidence from Clinical Trials: Some trials suggest that lowering blood glucose improves electrophysiologic measures in type 2 diabetics. In the Ohkubo trial, after 6 years of follow-up, the conduction velocity in the median nerve was 3.0-3.5 m/s higher in the intensive treatment group and the arm vibration threshold was lower, statistically significant differences ($p < 0.05$), but other physiological measures (leg vibration threshold, postural hypotension, electrocardiographic indices) were similar between groups and neurologic symptoms were not measured. A smaller Japanese trial also reported improved motor nerve conduction velocity (Kawamori and Kamada, 1991).

In contrast, the UKPDS noted no significant differences in the incidence of absent ankle and knee reflexes in conventionally and intensively treated patients. The incidence of biothesiometer measurements greater than 25 volts from both toes was significantly lower in the intensively treated group after 9 years of intensive treatment (relative risk = 0.60). The incidence of impotence, and of heart rate responses to deep breathing and standing, did not differ between the groups, although the basal heart rate was lower in intensively treated patients who were followed for 12 years (UKPDS 1998, 33).

Clinical Trial Evidence from Type 1 Diabetes Mellitus

Several clinical trials involving patients with type 1 diabetes have shown that intensive lowering of blood glucose concentrations can dampen the decrease in the conduction velocity observed in certain nerves (e.g., tibial, peroneal, sural) when compared with conventional insulin treatment (Dahl-Jørgensen et al., 1986; Reichard et al., 1996; Diabetes Control and Complications Trial Research Group, 1995 [b]).

The DCCT reported a statistically significant 69% reduction (from 9.8 to 3.1/100 patient-years) in the incidence of new "confirmed clinical neuropathy" (defined as an abnormal neurologic history or physical examination combined with abnormal nerve conduction or autonomic nervous system studies), but the incidence of neurologic symptoms themselves was not reported (Diabetes Control and Complications Trial Research Group, 1993; Diabetes Control and Complications Trial Research

Group, 1995[c]). The progression of clinical neuropathy in patients with preexisting disease was reduced by 57%, from 16.1 to 7.0/100 patient-years. The Stockholm trial reported at 7.5 year follow-up that new neurologic symptoms occurred in one patient receiving intensive treatment and 5 patients treated conventionally, but the difference was not statistically significant (Reichard et al., 1993). By 10 years, neuropathic symptoms were reported by 14% and 32% of intensively and conventionally treated patients ($p=0.04$), respectively, and pin prick sensitivity was also different ($p < 0.01$) (Reichard et al., 1996).

Nephropathy

Evidence from Type 2 Diabetes Mellitus

Observational Studies:

Some cross-sectional analyses indicate that patients with type 2 diabetes and elevated plasma glucose concentrations or glycosylated hemoglobin levels are more likely to have, at the same time, evidence of albuminuria (West et al., 1982; Mattock et al., 1988; Schmitz and Vaeth, 1988; Nelson et al., 1989; UKPDS Group, 1990; Gall et al., 1991; Savage et al., 1995) or renal histopathologic changes (Watanabe et al., 1987). In other cross-sectional analyses, the relationship between glycemic control and impaired renal function (abnormal creatinine clearance, elevated plasma creatinine, or proteinuria) is not statistically significant (Knuiman et al., 1986; Jerums et al., 1988).

Longitudinal studies suggest that type 2 patients with elevated FPG or glycosylated hemoglobin levels are more likely to develop new (or worsened) renal dysfunction in the future. Studies with follow-up periods as long as 20 years have found that a markedly elevated FPG concentration is a statistically significant predictor of persistent proteinuria (Ballard et al., 1988) and renal failure (Humphrey et al., 1989; Lee et al., 1994) (usually defined as a history of renal dialysis, transplant, and/or abnormal renal function). A study of 4400 patients found that average blood and urine glucose levels over time were predictive of future proteinuria (Pirart et al., 1978). In Pima Indians, baseline glucose tolerance test results predicted future proteinuria (Kunzelman et al., 1989). In a population-based retrospective cohort study of 1832 patients with type 2 diabetes in Rochester, Minnesota, a 100 mg/DL elevation in FPG was found to double the risk of developing chronic renal failure (95% CI=1.7-3.0) (Humphrey et al., 1989). The overall incidence of chronic renal failure in this population was 133/100,000 person-years.

The WESDR study, which followed over 1300 patients for an average of 10 years, found that although type 2 diabetic patients who were not taking insulin and had baseline glycosylated hemoglobin values in the third or fourth quartile were twice as likely to develop gross proteinuria (> 0.30 g/L) in the 10-year period, glycosylated hemoglobin values were not predictive in those patients taking insulin. Higher values were predictive when both groups were combined and insulin use placed in the model (Klein et al., 1995, 1996). Renal failure, which occurred in only 0-3% of patients, was not reliably predicted by glycosylated hemoglobin values (Klein et al., 1995).

Evidence from Clinical Trials:

There is evidence from two small clinical trials that intensive insulin treatment of patients with type 2 diabetes can reduce the incidence of albuminuria. A small Japanese trial (N=50) comparing multiple insulin injections with conventional treatment reported that, after 48 months, urinary protein excretion was over 150 mg/d lower for patients in the intensively treated group, a statistically significant difference (Kawamori and Kamada, 1991). A somewhat larger Japanese randomized trial (N=110) reported a statistically significant difference in the cumulative percentage of patients who progressed to micro- or macroalbuminuria over 6 years (28% versus 8% in the primary prevention group, 32% versus 12% in the secondary prevention group) (Ohkubo et al, 1995). During the 6-year period, only 4 patients in the control group developed clinical albuminuria (> 300 mg/24 hours).

The UKPDS also observed a significant difference in the incidence of microalbuminuria (urinary albumin concentration greater than 50 mg/L) between conventionally and intensively treated patients within 3 years of follow-up. The incidence of gross proteinuria (urinary albumin concentration greater than 300 mg/L) and of a two-fold increase in plasma creatinine became significantly lower with intensive treatment after 9 years of follow-up (relative risk reduction of 33% and 60%, respectively). The incidence rates for renal failure and death from renal disease did not differ significantly between the groups, but the absolute number of cases over the course of the study was small (25 and 10, respectively) (UKPDS 1998, 33).

Clinical Trial Evidence from Type 1 Diabetes Mellitus

Randomized controlled trials in type 1 diabetes suggest that intensive insulin therapy to lower blood glucose can significantly decrease urinary albumin excretion (UAE) rates. Of those in the primary prevention group of the DCCT who lacked microalbuminuria at baseline (with microalbuminuria defined as $\text{UAE} \geq 40 \text{ mg}/24 \text{ hr}$), the incidence of microalbuminuria over 6.5 years was reduced from 3.4 to 2.2/100,000 patient-years with intensive treatment, a relative reduction of 34% ($p < 0.04$), but the incidence of sustained microalbuminuria (abnormal on two successive annual evaluations), macroalbuminuria, or abnormal creatinine clearance was not significantly different. In the secondary prevention group, the incidence of microalbuminuria was reduced from 5.7 to 3.6/100,000 patient-years, a relative reduction of 43%, and the incidence of sustained microalbuminuria and of macroalbuminuria ($\text{UAE} \geq 300 \text{ mg}/24 \text{ hrs}$) was also significantly reduced ($p < 0.01$) (Diabetes Control and Complications Trial Research Group, 1993, 1995 [d]).

The Stockholm trial reported that over 7.5 years albuminuria ($\text{UAE} > 200 \mu\text{g}/\text{min}$) occurred in 2% of the intensively treated and 17% of the conventionally treated patients, respectively, a statistically significant difference ($p=0.01$) (Reichard et al., 1993) that was still present at 10-year follow-up (Reichard et al., 1996). At 7.5 years, the UAE had increased by 56 $\mu\text{g}/\text{min}$ with standard therapy and decreased by 11 $\mu\text{g}/\text{min}$ with intensive treatment ($p=0.04$), but glomerular filtration rates were unchanged (Reichard et al., 1993). At 10 years, the glomerular filtration rates remained unchanged (Reichard et al., 1996). Smaller trials in Norway and Denmark reported no significant effect on UAE or glomerular filtration rate at latest follow-up but may have lacked statistical power to detect a difference (Dahl-Jørgensen et al., 1992; Beck-Nielsen et al., 1990). A meta-analysis of trials published as of 1993, excluding the DCCT, concluded that intensive therapy lowered the risk of nephropathy by 66% (95% CI=42-80%) (Wang et al., 1993).

MACROVASCULAR OUTCOMES

Evidence from Type 2 Diabetes Mellitus

Observational Studies

Heart Disease. Cross-sectional studies of patients with type 2 diabetes report that elevated FPG concentrations or glycated hemoglobin levels are more common in persons with coronary artery disease (e.g., history of prior angina or myocardial infarction) (Welborn et al., 1984), an abnormal electrocardiogram (Hillson et al., 1984 [b]; UKPDS, 1990), or cardiovascular disease (Welborn et al., 1984). This association tends to persist even after adjustment for confounding variables associated with heart disease. Other cross-sectional studies report the absence of such an association, whether for cardiovascular disease in general (Standl and Janka, 1985; Nielsen and Ditzel, 1985; Meigs et al., 1997), nonfatal cardiac events (Paisey et al., 1984), or myocardial infarction (UKPDS, 1990).

Longitudinal cohort studies report that patients with elevated blood glucose, glycated hemoglobin, or postprandial glucose levels at baseline are more likely to develop coronary artery disease (Fu et al., 1993; Hanefeld et al., 1997; Turner et al., 1997) or an abnormal electrocardiogram (Fu et al., 1993) or that they are more likely to die from coronary artery (Moss et al., 1994; Fuller et al., 1983; Kuusisto et al., 1994 [a]; Andersson and Svärdsudd, 1995; Gall et al., 1995) or cardiovascular (Uusitupa et al., 1993; Andersson and Svärdsudd, 1995; Standl et al., 1997) disease. These associations persist even in multivariate analyses that adjust for other cardiac risk factors.

Stroke. The evidence of an association between blood glucose concentration and stroke is more limited. One cross sectional study found no such association (Welborn et al., 1984). Some cohort studies report that patients with elevated FPG or glycated hemoglobin levels are more likely to experience stroke (Kuusisto et al., 1994 [b]) or die from it (Moss et al., 1994), even after adjustment for confounding risk factors. Other cohort studies with sample sizes as large as 18,000 report no significant association with either stroke incidence (Fu et al., 1993) or stroke mortality (Fuller et al., 1983).

Peripheral Vascular Disease. There is limited observational evidence of an association between glycemic control and the incidence or symptoms of peripheral vascular disease (e.g., amputation, ulceration). Cross-sectional analyses have reported that elevated blood glucose concentrations are more common among persons with peripheral vascular disease (Welborn et al., 1984) and absent pedal pulses (UKPDS, 1990), while others report no such association, either with peripheral vascular disease (Paisey et al., 1984) or intermittent claudication (UKPDS, 1990). A case-control study reported that a glycated hemoglobin value greater than 9% was associated with a 70% increase in the risk of amputation, but the 95% confidence interval encompassed 1.0 (Reiber et al., 1992).

The WESDR study, a prospective cohort study involving 1300 patients, demonstrated a significant association between glycated hemoglobin levels at baseline and the subsequent incidence of amputation and foot ulcers (Moss and Klein, 1992). A 10-year prospective cohort study involving 1012 Native Americans reported an association between baseline FPG concentration and subsequent first lower extremity amputation that, in multivariate analysis, was statistically significant only for men (Lee et al., 1993). Finally, a 4-year prospective study involving 479 Taiwanese patients reported

that glycated hemoglobin was not significantly predictive of future lower extremity vascular disease (defined as intermittent claudication or amputation) (Fu et al., 1993).

Evidence from Clinical Trials

The UKPDS reported a 16% reduction in the 10-year incidence of myocardial infarction when patients receiving intensive treatment (mean glycated hemoglobin = 7.0%) were compared with conventionally treated patients (mean glycated hemoglobin = 7.9%). This difference achieved borderline statistical significance ($p = 0.05$, 95% confidence interval for relative risk = 0.71-1.00) (UKPDS 33; 1998), although statistically significant differences were noted in certain subgroups (UKPDS 34; 1998). Sudden death was significantly lower (relative risk reduction of 46%, $p = 0.05$). The incidence of fatal myocardial infarction, heart failure, angina, stroke, amputation, and death from peripheral vascular disease was not significantly lowered (UKPDS 1998, 33). With respect to fatal outcomes, the authors noted that the study lacked sufficient statistical power to exclude a beneficial effect.

The Veterans Administration trial reported no significant difference in cardiovascular mortality or cardiovascular events in the intensive treatment group, but the mean follow-up period was only 27 months (Abaira et al., 1997). A seemingly higher proportion of cardiovascular events in the intensive treatment group (32% versus 20%) was not statistically significant. A regression model indicated that a lower glycated hemoglobin level prior to the event was the only significant correlate for new cardiovascular events. A British trial involving 248 patients with moderate hyperglycemia reported that cardiovascular events occurred less frequently in a group given a higher dose of tolbutamide and a recommended diet than in the control group, but the patient population, type of diabetes, and outcome measures were imprecisely defined (Keen et al., 1968).

Clinical Trial Evidence from Type 1 Diabetes Mellitus

In the DCCT, the incidence of all major cardiovascular and peripheral vascular events was low in the conventionally and intensively treated groups (0.8 and 0.5 events/100 patient-years, respectively) and did not differ significantly (DCCT, 1993). The Stockholm study reported no significant difference in the incidence of myocardial infarction or myocardial perfusion (as measured by digital plethysmography) in the intensively treated group (Reichard and Pihl, 1994). Neuropathic foot ulcers occurred in no patient receiving intensive treatment and 3 treated conventionally, but the difference was not statistically significant (Reichard et al., 1993). Subsequent angiographic analysis in some of the trial subjects suggested that the carotid artery was thinner and less stiff in intensively treated patients than in controls (Jensen-Urstad et al., 1996).

ALL-CAUSE MORTALITY

Evidence from Type 2 Diabetes Mellitus

Observational Studies:

A modified cross-sectional study reported an association between mean FPG concentrations and overall survival rates in type 2 diabetes (Muggeo et al., 1995), and cohort studies report that adjusted all-cause mortality rates are significantly higher for patients with elevated baseline FPG

concentrations (Andersson and Svärdsudd, 1995; Sasaki et al., 1997), mean FPG concentrations over time (Andersson and Svärdsudd, 1995), glycosylated hemoglobin levels (Moss et al., 1994; Gall et al., 1995), or postprandial glucose concentrations (Hanefeld et al., 1997). However, other cohort studies report that death rates are not reliably predicted by FPG concentrations (Hadden et al., 1986) or glycosylated hemoglobin levels (Davis et al., 1988).

Evidence from Clinical Trials:

The only prospective evidence that glycemic control lowers all-cause mortality is a Swedish randomized controlled trial involving 620 patients with diabetes who had been admitted to coronary care units for recent myocardial infarction (DIGAMI trial). The patients were randomized to an experimental group, which received an insulin-glucose infusion for the first 24 hours and subcutaneous insulin four times daily for three months, or to a control group that received standard treatment. A statistically significant separation in glycosylated hemoglobin levels was noted at the third and twelfth month of follow-up. Over a mean follow-up period of 3.4 years, the all-cause mortality rates in the experimental and control groups were 33% and 44%, respectively ($p = 0.01$) (Malmberg, 1997).

In the UKPDS, all-cause mortality was 18.9/1000 patient-years in conventionally treated patients and 17.9/1000 patient-years in intensively treated patients, a difference that was not statistically significant. The incidence of diabetes-related deaths also did not differ significantly (UKPDS 1998, 33). As already noted, the study lacked statistical power to exclude a beneficial effect on fatal outcomes.

Clinical Trial Evidence from Type 1 Diabetes Mellitus

There are few data on all-cause mortality in type 1 diabetes because of the low event rate. In the DCCT, there were 7 deaths in the intensively treated group and 4 deaths in the conventional group, a difference that was not statistically significant (DCCT, 1993). The Stockholm trial reported 4 deaths in patients receiving intensive therapy and 3 deaths in those receiving conventional treatment (Reichard and Phil, 1994).

WEIGHING THE MAGNITUDE OF BENEFIT

Observational evidence of the association between blood glucose levels and the complications of diabetes are of limited value in proving that lowering blood glucose significantly reduces the incidence of such complications and are not reviewed in detail here. Clinical trial evidence is more persuasive, and it suggests that the incidence of microvascular complications can be lowered by improved glycemic control. In trials involving patients with both type 1 and type 2 diabetes, glycemic control has been shown to significantly reduce the incidence of retinopathy, peripheral neuropathy, and nephropathy.

The following points should be considered when applying the results of these clinical studies to routine practice: First, the intensity of treatment shown to be efficacious in clinical trials may be difficult to replicate to the same degree in normal practice conditions. In the DCCT, patients received insulin by injection three times daily or by external pump, self-monitored blood glucose at least four

times per day, underwent weekly nocturnal blood glucose measurements, visited their study center every month, and received even more frequent telephone contacts (Diabetes Control and Complications Trial Research Group, 1993). The target glycosylated hemoglobin value was less than 6.1%. In other trials of patients with type 1 diabetes, intensive treatment was achieved by continuous subcutaneous insulin infusion, an intervention that cannot be easily replicated in normal practice. However, more typical treatment approaches were used in the UKPDS.

Well-designed quality improvement programs at certain health care systems have been successful in achieving satisfactory blood glucose levels in patients with type 2 diabetes in routine clinical practice by using a variety of practice and organizational tools. Constraints imposed by health care systems and/or the inability or reluctance of patients to adhere to treatment protocols may limit the capacity of providers to achieve optimal treatment goals, however. A large cohort study at a health maintenance organization reported that 60% of patients with type 2 diabetes had glycosylated hemoglobin levels of 8% or greater two years after starting insulin therapy (Hayward et al., 1997). These patients were cared for in 1990-1993, however, and efforts to achieve glycemic control may have improved after the release of the DCCT in 1993 and the introduction of new oral drugs for type 2 diabetes. A report from the Provider Recognition Committee of the American Diabetes Association indicates that of the first 160 physicians achieving recognition for providing quality diabetes care, the mean hemoglobin A_{1c} level of a representative sample of their patients (N = 4462) was 7.8% (SD = 1.7%) (ref in preparation).

Second, the microvascular complications affected in clinical trials are mostly intermediate or surrogate endpoints rather than health outcomes of obvious clinical relevance to patients. (Of course, in many patients these intermediate endpoints subsequently progress to perceptible clinical outcomes, which do have relevance to patients.) Investigators have measured statistically significant changes in the incidence of retinal hemorrhages and exudates (retinopathy), treatments for eye disease (photocoagulation, cataract extraction), nerve conduction velocity (neuropathy), and urinary albumin excretion rates (nephropathy), but there is limited direct evidence from clinical trials about incidence rates for symptoms that patients experience, such as reduced visual acuity, numbness and paresthesias, or the complications of renal failure. However, many of the studies lacked the design and follow-up periods to detect such effects.

Many of the intermediate/surrogate outcomes in which changes have been detected are important risk factors for progression to clinically meaningful symptoms--e.g., patients with diabetic retinopathy, especially if proliferative, are significantly more likely to develop visual impairment or blindness than those without retinopathy¹¹--but a statistically significant reduction in the incidence of intermediate outcomes does not necessarily translate into a significant effect on symptoms perceptible to patients. Of course, such complaints generally do not occur until the patient develops end-stage disease. In the case of retinopathy, decreased vision may not occur because of laser treatment given based on the retinal findings. Conversely, laser therapy can result in night blindness and diminished peripheral vision. Thus, the current lack of evidence does not prove or disprove a major effect on health outcomes.

¹¹ Macular edema is an even greater risk factor for visual impairment in type 2 diabetes.

Third, even if it is accepted that improved glycemic control does reduce the incidence of disease symptoms perceptible to patients, the absolute number of patients affected may be limited. For example, the DCCT reported a 76% reduction in the *relative* risk of retinopathy, from 4.7 to 1.2 events/100 patient-years. These events occurred over 6.5 years in 91/378 (24%) of conventionally treated patients and 23/348 (9%) of intensively treated patients, a difference in *absolute* risk of 15% (Diabetes Control and Complications Trial Research Group, 1993). The 25% reduction in the relative risk of microvascular complications reported by the UKPDS (from 11.4 to 8.6 events/1000 patient-years) (UKPDS 1998, 33) represents an absolute reduction of only 2% (from 121/1138 [10%] to 225/2729 [8%]) over 10 years of treatment. Moreover, probability estimates in most trials refer to intermediate outcomes; the 76% reduction in the risk of retinopathy reported by the DCCT relates to how frequently a 3-step change was observed on a 25-item retinopathy scale, not to improvements in vision. Reported improvements in neuropathy refer mostly to meters per second in nerve conduction velocity.

The number-needed-to-treat to achieve a reduction in outcomes perceptible to patients would be far higher than those reported in the UKPDS and DCCT, because only a subset of patients with retinopathy, delayed nerve conduction, or elevated UAE are destined to develop symptomatic disease. For example, the reported incidence of chronic renal disease in the type 2 population is 133/100,000 person-years (Humphrey et al., 1989), far lower than the incidence of albuminuria. Based on these data and the 44% reduction in relative risk reported by the DCCT (for preventing gross albuminuria¹²), it can be calculated that 1695 patient-years of intensive glycemic control would be required to prevent one case of chronic renal failure. Based on UKPDS data, 37 patients would require intensive treatment for an average of 10 years to prevent one patient from undergoing laser treatment; 208 would require treatment to prevent one case of blindness¹³ (UKPDS 1998, 33).

On the other hand, when examined at the population level, even modest absolute risk reductions can translate into large numbers of persons in society for whom clinical benefit is achievable. Given the millions of persons in the United States with type 2 diabetes, even a 2% absolute reduction in the risk of microvascular complications represents many thousands of persons whom would benefit from glycemic control equivalent to the DCCT or UKPDS.

Fourth, a percentage of patients who would benefit from the prevention of microvascular complications may not live long enough because of competing risks of death from macrovascular complications and other comorbid disease. The duration of diabetes is an important factor in the pathogenesis of microvascular disease, and years of intensive glycemic control are required before a difference in outcomes is observed. On average, less time is available for this process in patients with type 2 diabetes, because the disease appears later in life¹⁴ and because such patients are at greater risk

¹² Which certainly overstates the probability of preventing chronic renal failure.

¹³ The observed 16% difference in the incidence of blindness in the UKPDS between conventionally and intensively treated groups was not statistically significant.

¹⁴ The observed 16% difference in the incidence of blindness in the UKPDS between conventionally and intensively treated groups was not statistically significant.

of premature death from coronary artery disease and strokes. Although elevated blood glucose levels may be a risk factor for cardiovascular disease, clinical trials have not definitively shown that lowering blood glucose levels is protective. The UKPDS reported a 16% reduction in myocardial infarction of borderline statistical significance (UKPDS 1998, 33). One clinical trial (Malmberg, 1997) found that improved glycemic control (with insulin in patients with myocardial infarction) significantly reduced the incidence of ischemic cardiac events, stroke, or cardiovascular deaths. Two others (Ohkubo et al., VA Cooperative) may have lacked adequate duration or sample size to detect an effect.

The magnitude of benefit is also contingent on other patient-specific factors. Chief among these are the patient's level of glycemic control at baseline and the length of time that hyperglycemia has been present. In general, absolute risk reductions are greater for patients with high levels of glycated hemoglobin than for those with mild elevations (Hayward et al., 1997). Although it is of obvious importance for clinicians to prevent patients' progression from mild (e.g., hemoglobin A_{1c} levels of 6-8%) to marked hyperglycemia (e.g., hemoglobin A_{1c} levels > 9.5%), in those patients who have already developed very high glucose levels efforts directed at achieving even moderate glycemic control (e.g., hemoglobin A_{1c} levels of 8-9.5%) will result in greater health benefits than the pursuit of euglycemia in patients with moderate elevations.

Thus, different kinds of patients with type 2 diabetes will benefit differently from improved glycemic control. The probability of benefit for each of the different subgroups of patients, and their clinical importance to the individual, must be weighed against the potential life disruption, adverse effects of treatment, and monetary and non-monetary costs in order to fully assess the benefit-risk ratio.

POTENTIAL HARMS OF INTENSIVE GLYCEMIC CONTROL

Specific complications in addition to hypoglycemia can occur with each of the agents used to treat type 2 diabetes. As with most pharmaceuticals, insulin has potential adverse effects and oral drugs to reduce glycemia (sulfonylureas, metformin, acarbose, troglitazone) carry some risk of undesirable side effects (e.g., flatulence, diarrhea) and highly uncommon, more serious complications (e.g., lactic acidosis, hepatotoxicity). A detailed listing of all potential side effects of diabetic medications and of their reported probability rates is beyond the scope of this review.

Hypoglycemia

Evidence about the magnitude and statistical significance of the risk of hypoglycemia and its complications is inconsistent across clinical trials. Furthermore, the risk of severe hypoglycemia appears to differ between patients with type 1 and type 2 diabetes, being greater in the former and therefore not reviewed here. Some trials involving patients with type 2 disease reported an increased risk for minor hypoglycemic episodes. In the Veterans Administration trial, the incidence of mild to moderate hypoglycemia (16.5 versus 1.5 patients/year) was greater in patients receiving intensive treatment ($p < 0.001$), but the incidence of severe episodes was low and did not differ significantly (Abaira et al., 1997).

¹⁴ As noted earlier, although the *average* age of onset is later for type 2 than for type 1 diabetes, a significant proportion of patients with type 2 diabetes do live long enough to experience microvascular complications.

In the UKPDS, the incidence of major hypoglycemic episodes was higher among intensively treated than among conventionally treated patients ($p < 0.0001$), but the rates were low in both groups (1-2% versus 0.7%, respectively). The incidence of any hypoglycemic episode, including minor events, was higher among intensively treated patients than among controls. Among those taking insulin, each year about 3% had a major episode and 40% a minor or major episode. There was only one death from hypoglycemia in 3867 patients followed over 10 years (UKPDS 1998, 33).

A recent cohort study of 8668 patients with type 2 diabetes provides data from community practice at a large health maintenance organization. Although patients taking sulfonylureas were no more likely to report symptoms attributed to hypoglycemia (e.g., sweating, weakness, trembling, insulin reaction) than those not receiving hypoglycemic medications, 17% of patients receiving insulin reported that such symptoms occurred weekly. Thirty-eight percent reported that hypoglycemic symptoms occurred at least two to three times per month; 23% reported never having such symptoms. Insulin therapy was not associated with increased emergency department visits or hypoglycemia-related hospitalizations (Hayward et al., 1997).

Weight gain

Several trials have reported an association between intensive treatment and weight gain. The DCCT noted a 33% increase (12.7 versus 9.3 cases/100 patient-years) in the risk of becoming overweight (20% greater than desirable body weight) (DCCT, 1993). At five years, patients in the intensive treatment group had gained an average of 4.6 kg more than those receiving conventional therapy. In the Oslo Study, body weight over 2 years was higher in the multiple injection group than in the continuous and conventional treatment groups (Dahl-Jorgensen, 1986). In the UKPDS, weight gain was an average of 3.1 kg higher among patients intensively treated with insulin or sulfonylureas than among controls (UKPDS 1998, 33). There is no evidence that this amount of weight gain in an obese individual significantly impacts on outcomes. In fact, the intensively treated patients in the UKPDS appeared to have borderline improvement in some cardiovascular outcomes.

Other adverse effects

Intensive glycemic control generally requires patients to closely monitor their blood glucose levels at home, often on a daily basis; follow careful dietary restrictions and increased physical activity; tolerate minor side effects and the risk of more serious complications from medications; visit the doctor on a regular basis for testing and examinations; and absorb out-of-pocket costs not covered by insurance for physician services and medical supplies, lost work (or school) time, and transportation. Although the influence attributable to insulin versus glycemic control is unclear, a cohort study found that insulin users had more laboratory tests performed, 2.4 more outpatient visits per year, and almost 300 more fingersticks for home glucose monitoring than patients using sulfonylureas (Hayward et al., 1997). In many cases these inconveniences, discomforts, and costs must be borne over a number of years, often a lifetime. There are currently few reliable data on which to measure the magnitude of these problems, their relative importance to patients, or the degree to which they are offset by the benefits of treatment. The DCCT found no association between intensive treatment and lower quality of life (DCCT, 1996). A recent study suggested that the net effect of improved glycemic control is

improved quality of life and work productivity and decreased absenteeism and unemployment (Testa and Simonson, 1998).

OUTCOME ESTIMATES

It is useful for practice guidelines to estimate the comparative probability of benefits and harms. Because the magnitudes of the benefits and harms of glycemic control depend on a variety of patient-specific variables, general estimates from clinical trials are not uniformly applicable to individual patients. Mathematical models have been developed to provide such estimates. For example, a model based on data from the DCCT and other sources estimated that patients with type 2 diabetes who maintained a glycated hemoglobin level of 7.2% would reduce the cumulative incidence of blindness, end-stage renal disease, and lower extremity amputation by 72% (from 19% to 5%), 87% (from 17% to 2%), and 67% (from 15% to 5%), respectively. Life expectancy would increase by 1.39 years (Eastman et al., 1997). Using a Markov model based primarily on the DCCT, Vijan et al. (1997) estimated that reducing glycated hemoglobin from 9% to 7% in a patient in whom diabetes developed at age 45 would lower the lifetime risk of blindness from 2.6% to 0.3%. The same change in a patient with diabetes onset at age 65 would decrease the risk of blindness from only 0.5% to < 0.1% (Vijan et al., 1997). Accordingly, a physician might approach patients in these age groups very differently, especially if the 65 year-old person already had a complication of diabetes or a major comorbid disease.

Ideally, these modeling data could be used to develop outcome tables that clinicians and patients could consult to estimate the benefits and harms of different levels of glycemic control for individual clinical scenarios. Available models, however, produce discrepant results about the likely outcomes of glycemic control in the same patient. For a 55-year-old Caucasian patient who lowers his or her glycated hemoglobin level from 9% to 7%, for example, the Eastman model estimates that the lifetime risk of blindness would be reduced from 9% to 3.4%, whereas the Vijan model estimates that it would be reduced from 1.2% to 0.1%. Accordingly, the absolute risk reduction for this scenario differs considerably between the Eastman and Vijan models (5.6% versus 1.1%, respectively).

Some of these discrepancies relate to fundamental differences in the design, assumptions, and data employed in the models. The investigators are currently updating their models to address these discrepancies. We expect that their efforts and our own will ultimately enable the production of explicit outcome tables that patients and clinicians can use to estimate the likely outcomes of glycemic control.

CONCLUSIONS

The evidence demonstrates a continuous and curvilinear relationship between hyperglycemia and the microvascular and neuropathic complications of diabetes, with risk rising progressively as mean blood glucose concentrations increase. The data indicate that patients with type 2 diabetes benefit from the control of blood glucose levels. The potential magnitude of absolute risk reduction varies as a continuous variable, however, depending on: the (a) patient's current glycated hemoglobin level and (b) duration and magnitude of prior hyperglycemia; and (c) extent of preexisting microvascular complications. A critical variable is the patient's glycated hemoglobin level; individuals with marked elevations generally benefit more (in reduced absolute risk of complications) from the same absolute

reduction in glycosylated hemoglobin levels than do individuals with mild-moderate elevations. The probability that the patient will live long enough to experience the benefits of reduced complications depends on (d) cardiovascular risk factors other than blood glucose (e.g., tobacco use, blood pressure, serum lipid levels, physical activity, obesity, preexisting coronary artery disease) and (e) other determinants of life expectancy (e.g., age, coexisting diseases, health status).

The evidence demonstrates that, for an individual with type 2 diabetes, the better the glycemic control, the lower the probability of developing chronic microvascular and neuropathic complications (and, possibly, cardiovascular complications). However, because of differences in patients' life expectancies and comorbidities, it is inappropriate to set a uniform target glycosylated hemoglobin level for all patients with type 2 diabetes. Individuals with long life expectancies and few comorbidities may wish to pursue euglycemia, but less vigorous goals may be appropriate in elderly individuals with multiple comorbid conditions and/or limited life expectancies.

Whether the magnitude of benefit of a given treatment goal justifies the potential inconvenience, harms, and costs involves value judgments that must be tailored to the individual patient. Patients' personal risk profiles and capabilities and the relative importance they assign to the potential outcomes and supporting evidence are integral to determining how intensively to treat.

Cardiovascular disease is the most likely cause of death in patients with type 2 diabetes, and thus attention to glycemic control should not distract clinicians and patients from other interventions that may be far more effective in preventing coronary artery disease and stroke, such as smoking cessation, serum lipid management, control of blood pressure, diet, physical activity, and weight management. Guidelines for the detection and management of these risk factors are published elsewhere (Fiore et al., 1996; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 1993; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997). Clinicians should also give due attention to treatments other than glycemic control for preventing microvascular complications (e.g., blood pressure control and use of angiotensin converting enzyme inhibitors for diabetic nephropathy).

Regardless of the treatment goal and of choices about the intensity of glycemic control, patients face considerable barriers in implementing recommendations to modify diet and other personal lifestyle habits; comply with self-monitoring, medication, and home care instructions; and return for follow-up visits. Physicians should work with patients to identify and design solutions for remediable barriers and should utilize recommended techniques for patient education and counseling (Roter et al., 1998) to give patients the factual information and motivational encouragement they need for meaningful change.

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Table 1. Randomized controlled trials of intensive versus conventional insulin treatment in type 2 and type 1 diabetes

Study	Location	Inclusion criteria	N	Intervention	Follow-up (yrs)	Glucose control (HbA1c, %)
Type 2 diabetes						
UKPDS	Britain	Type 2, newly diagnosed, with FPG of 6.1-15.0 mmol/L (110-270 mg/dl) after 3 months of dietary treatment	2729	Diet + sulfonylureas, insulin, metformin (see text)	10	7.0
			1138	Diet		7.9
Ohkubo et al.	Japan	Type 2, 1-2 injections/d, no/mild retinopathy, UAE < 300 mg/24h, creatinine < 1.5 mg/DL, no neuropathy, age < 70, no DKA, negative islet cell antibody, urinary C-peptide > 20 µg/d	26 PP 26 SP	≥ 3 injections/day	6	7.1
			25 PP 25 SP	1-2 injections per day		9.4
UGDP*	U.S.	Type 2, newly diagnosed, abnormal GTT, free of major diabetic symptoms (eg DKA) for weeks on diet alone	204	IVAR: insulin dose titrated to glucose level	12.5	140**
			210	ISTD: dose based on body surface		190**
			205	Diet alone		192**
VA CSDM	U.S.	Type 2, male, age 40-69, suboptimal glucose control, and no recent MI, CHF, amputation, or renal disease	75	Stepped regimen (from 1 to > 3 injections/d), including insulin and sulfonylureas	2.3	7.1
			78	1 injection/d		9.2
Type 1 diabetes						
DCCT	U.S.	Type 1; age 13-39; no hypertension, high blood cholesterol, severe diabetic or medical condition	348 PP 363 SP	External insulin pump or ≥ 3 injections/day, monthly visits, telephone contact, team approach	6.5	7.2
			378 PP 352 SP	1-2 daily injections, daily self-monitoring, education		9.1
Stockholm trial (Reichard et al.)	Sweden	Type 1, nonproliferative retinopathy, normal creatinine, poor glucose control	48	3 injections/d (82%), education, tutoring	7.5	7.2
			54	Routine care, MD visits q 4m, 2-3 injections/d		8.3
Kroc Collaborative	U.S./U.K	Type 1, urinary C-peptide negative, mild-moderate proliferative retinopathy	34	CSII, frequent self-monitoring	2	≈9
			34	CIT		≈10.5
Kawamori et	Japan	1-2 injections/d, early microvascular complications,	28	Multiple injections/day	6.4	≈8.5

al		urinary C-peptide < 20 µg/d	22	1 injection/day		≈10
Eschwege et al	France	Type 1	21	2-3 injections/day	4.2	166**
			21	1 injection/day		192**
Steno I	Denmark	Age 18-51, C-peptide < 0.2 nmol/l, duration of diabetes 5-35 y, onset before age 30, no renal dysfunction	18	CSII	8	7.6
			16	CIT		8.1
Steno II			18	CSII	5	7.9
			17	CIT		8.8
Oslo Study Group	Norway	Type 1, C-peptide < 0.1 nmol/L	15	CSII	2	8.7
			15	Multiple injections/day		9.1
			15	2 injections/day		10.2
Beck-Nielsen et al	Denmark	Type 1, no/minor retinopathy, no nephropathy, age 18-41, diagnosis for 5-20 y, no meds except insulin	12	CSII	5	7.4
			12	2 injections/day		8.9

CIT=conventional insulin therapy; CSII=continuous subcutaneous insulin infusion; PP=primary prevention group; SP=secondary prevention group

* The original UGDP study included treatment arms for tolbutamide and phenformin but these were discontinued due to adverse event rates.

**Mean FPG, mg/dL

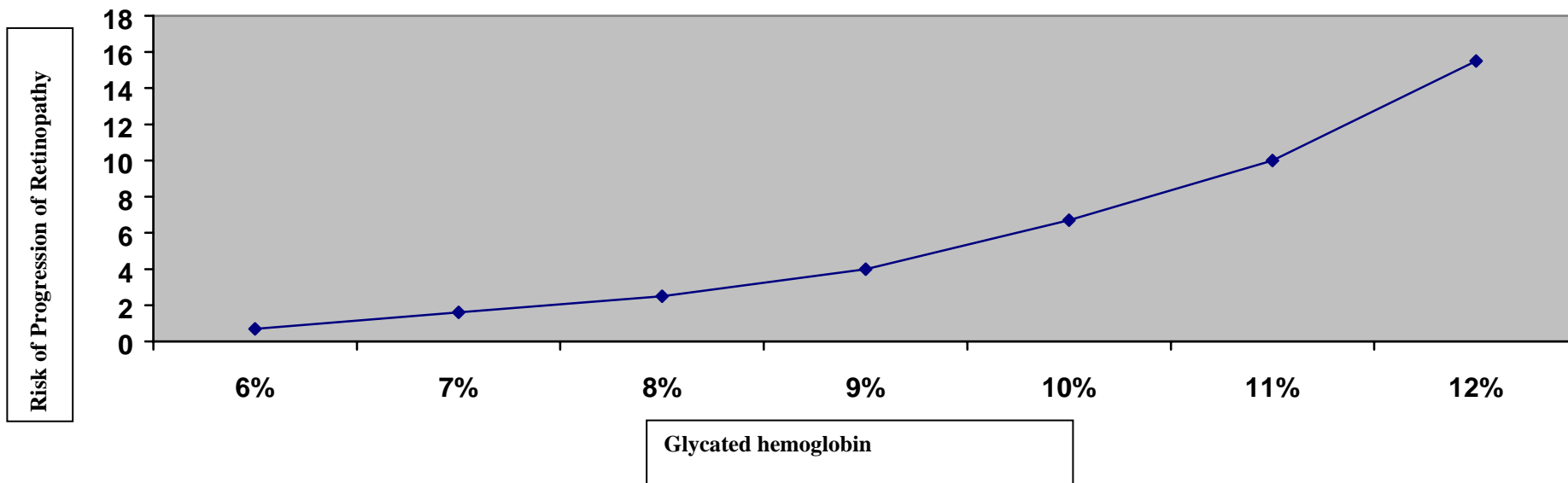
Table 2. Incidence and Progression Rates of Retinopathy from Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)

H _g A _{1c}	4-Year Incidence						10-Year Incidence					
	Any retinopathy		Progression of retinopathy		Progression to proliferative retinopathy		Any retinopathy		Progression of retinopathy		Progression to proliferative retinopathy	
	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)
Onset Over Age 30, Taking Insulin												
1 st quartile	38.8	1.0 (NA)	24.5	1.0 (NA)	3.8	1.0 (NA)	70.4	1.0 (NA)	54.9	1.0 (NA)	12.3	1.0 (NA)
2 nd quartile	43.6	1.1 (0.7-1.9)	25.8	1.1 (0.6-1.7)	3.4	0.9 (0.2-3.9)	80.6	1.1 (0.7-1.7)	59.3	1.1 (0.8-1.6)	18.5	1.2 (0.5-2.9)
3 rd quartile	46.4	1.2 (0.7-2.0)	32.3	1.3 (0.8-2.1)	6.4	1.7 (0.5-5.8)	79.6	1.1 (0.7-1.8)	72.7	1.4 (1.0-1.9)	24.2	2.0 (1.0-4.3)
4 th quartile	74.1	1.9 (1.3-2.9)	52.2	2.1 (1.4-3.1)	15.2	4.0 (1.4-11.7)	100	1.9 (1.3-2.9)	86.6	2.1 (1.6-2.8)	37.9	3.1 (1.5-6.1)
Onset Over Age 30, Not Taking Insulin												
1 st quartile	12.9	1.0 (NA)	7.9	1.0 (NA)	1.8	1.0 (NA)	47.0	1.0 (NA)	30.7	1.0 (NA)	2.0	1.0 (NA)
2 nd quartile	28.8	2.2 (1.2-4.3)	15.5	2.0 (0.9-4.2)	0.9	0.5 (0-5.2)	57.2	1.4 (0.9-2.2)	45.7	1.8 (1.2-2.7)	2.4	1.2 (0.2-8.3)
3 rd quartile	49.3	3.8 (2.1-7.0)	31.0	3.9 (2.0-7.8)	0.9	0.5 (0-5.2)	83.9	2.5 (1.7-3.5)	66.8	2.8 (1.9-4.2)	9.6	4.0 (1.0-16.6)
4 th quartile	51.8	4.0 (2.2-7.4)	49.0	6.2 (3.2-12.0)	6.7	3.7 (0.8-17.3)	89.7	2.7 (1.9-4.0)	80.5	4.3 (3.0-6.2)	30.0	13.8 (4.8-39.5)

Legend: NA=not applicable

Adapted from: Klein R, Klein BEK. Vision disorders in diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, eds. Diabetes in America, 2nd ed. NIH Publication No. 95-1468. Rockville, MD: National Institutes of Health, 1995, (Table 14.25), p 314. RR = relative risk, CI = confidence interval. Glycated hemoglobin levels for those taking insulin: 5.9-8.8% (1st quartile), 8.9-10.2% (2nd quartile), 10.3-11.5% (3rd quartile), 11.6-17.0% (4th quartile); for those not taking insulin: 5.4-7.6% (1st quartile), 7.7-8.6% (2nd quartile), 8.7-10.0% (3rd quartile), 10.1-20.8% (4th quartile).

Figure 1. Absolute risk of retinopathy progression (hazard rate per 100 patient-years) as a function of glycated hemoglobin levels in the DCCT. Redrawn from Diabetes 1996;45:1289-98 (Figure 2B).



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