Chapter 39
Glycemic Goals

David J. Brillon

Introduction

Both type 1 and type 2 diabetes are accompanied by microvascular and macrovascular complications. For decades the association between chronic hyperglycemia and the development of long-term eye, kidney, and nerve disease was suspected based on animal models of diabetes[1–3] and the long-term observations of clinicians.[4] Nonetheless, the belief that normalization of blood glucose would prevent end organ damage was not universally accepted.[5]

By the 1980s several small prospective multicenter randomized trials were conducted to address this question. These studies were of short duration[6] or had conflicting results regarding the benefits of glycemic control on microvascular disease.[6–8] Indeed, achieving lower blood glucose levels appeared to worsen established retinopathy for the initial 8 months.[6]

Microvascular Disease

To definitively address the question of glycemic control and the development of diabetic microvascular disease, a large randomized interventional trial, which would eventually involve 29 centers in the US and Canada, was begun. A total of 1441 patients with type 1 diabetes were recruited from 1983 to 1989 to comprise the cohorts of the Diabetes Control and Complications Trial or DCCT.[9] Two cohorts were studied – a primary prevention cohort, to determine if intensive glycemic control would prevent the development of diabetic retinopathy, and a secondary intervention cohort to determine if intensive glycemic control would ameliorate the progression of early diabetic retinal disease. For the primary prevention cohort subjects had to have 1–5 years duration of diabetes, absence of retinopathy by fundus photography, and urinary albumin excretion <40 mg/24 h. The secondary intervention cohort criteria were 5–15 years duration of diabetes, mild (one microaneurysm) to moderate nonproliferative retinopathy, and urinary albumin excretion <200 mg/24 h. Patients were randomized to either conventional or intensive glycemic control. Intensive therapy included multiple (three or more) daily insulin injections (MDI) or continuous subcutaneous insulin injection (CSII) via an insulin pump. Insulin doses were adjusted according to fingerstick blood glucose (BG) values (obtained at least four times a day), dietary intake, and level of physical activity. The goal of intensive therapy included premeal BG levels 70–120 mg/dl, postprandial levels under 180 mg/dl, and hemoglobin A1c (HbA1c) levels within the nondiabetic range (<6.05%). To help achieve the goals, subjects met monthly with the physician, nurse educator, and dietician of the study and were contacted by telephone to review and adjust their regimen as necessary. Subjects randomized to conventional therapy received the usual diabetes treatment of the time, 1–2 insulin injections a day. The goals were to avoid symptomatic hypo- or hyperglycemia but not to achieve specific target glucose levels. Although subjects in the

D.J. Brillon (✉)
Division of Endocrinology, Diabetes and Metabolism, Weill Cornell Medical College, New York, NY, USA
e-mail: djbrillo@med.cornell.edu

L. Poretsky (ed.), *Principles of Diabetes Mellitus*, DOI 10.1007/978-0-387-09841-8_39,

conventional arm also received diet and exercise education, they only performed once daily glucose monitoring and met with the study team on a once every 3 month basis.

Both cohorts (a total of 1441 patients) were followed for a mean of 6.5 years. During this time seven field stereoscopic fundus photos, 24 h urine albumin excretion, clinical neuropathy assessment, peripheral nerve conduction studies, and autonomic nerve testing were performed. About 99% of the participants completed the study. From an initially statistically identical HbA1c at the beginning of the study, the intensively treated group reached a nadir of 6.9% at 6 months. Throughout the subsequent 6 years a statistically significant HbA1c separation (approximately 7.2% vs. 9.1%) between intensive and conventional therapy was maintained.

The trial was ended prematurely due to significant outcome differences between intensively and conventionally treated subjects. Outcome curves for retinopathy were initially similar but separated after 3 years. Intensive therapy decreased the mean risk of progression of retinopathy by 76% in the primary prevention and by 54% in the secondary intervention cohorts. In addition, the adjusted risk of proliferative or severe nonproliferative retinopathy was reduced by 47% and the need for photocoagulation by 56% in the secondary intervention group. Similarly, with regard to diabetic renal disease, intensive therapy resulted in significant reductions in risk of microalbuminuria of 34% (primary cohort) and 43% (secondary cohort). In the secondary intervention cohort, approximately 10% of whom had microalbuminuria at onset, the risk of albuminuria >300 mg/24 h was reduced by 56%. The appearance of clinical neuropathy (defined as the presence of signs or symptoms of peripheral neuropathy accompanied by either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic testing) was reduced with intensive therapy by 69% in the primary cohort and by 57% in the secondary intervention cohort. The reductions were significant for both peripheral and autonomic neuropathy.[10,11]

The positive reductions in cumulative incidence of microvascular complications were also analyzed within subgroups of the DCCT subjects defined on the basis of several baseline covariates to ensure consistency of results. These included age (adolescents versus adults), gender, duration of diabetes, baseline HbA1c, and mean blood pressure. The effect of intensive treatment was consistently maintained in all subgroups in both the primary and secondary cohorts. Thus the DCCT conclusively demonstrated that intensive glycemic control therapy delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in individuals with type 1 diabetes.

The DCCT was the largest and longest duration study of glycemic control in type 1 diabetes. Several months prior to its publication a study involving 102 subjects with type 1 diabetes in Sweden was published. As with the DCCT, subjects participating in the Stockholm Diabetes Intervention Study (SDIS) were randomized to intensive versus standard therapy and followed for 7.5 years.[12] Mean HbA1c levels were reduced from 9.4 to 8.5% in the standard treatment group and from 9.5 to 7.1% in the intensive treatment group. After 7.5 years both progression of nonproliferative retinopathy and the need for laser photocoagulation was less in the group receiving intensive control. There were more patients in the standard group with albumin excretion of at least 300 mg/24 h and with nephropathy as defined by subnormal glomerular filtration rates. Peripheral nerve conduction velocities deteriorated more in the standard treatment group. These results were the first to describe the beneficial effects of intensive therapy on retarding the development and progression of microvascular complications in patients with type 1 diabetes.

Based on the DCCT and SDIS studies published in 1993, most diabetes organizations advocated the use of intensive glycemic control therapy for all individuals with type 1 and type 2 diabetes.[13] The latter group was not studied in either trial. However, as the microvascular complications were all too similar in both types of diabetes[14,15] the extrapolation was applied. This recommendation was not universally accepted.[16,17] It was felt that the use of intensive insulin therapy in type 2 diabetes may lead to an increase in cardiovascular morbidity and/or mortality due to increased hypoglycemia, higher insulin levels, and/or greater weight gain. This concern had some basis in prior epidemiologic studies demonstrating that coronary artery disease (CAD) occurs with greater frequency in type 2 than in type 1 diabetes, a difference attributable not only to the older age of onset of type 2 diabetes but also to the dysmetabolic state that accompanies the disease.[18–20]

A group of investigators at Kumamoto University in Japan replicated the design of the DCCT, but in individuals with type 2 diabetes.[21] Fifty-five subjects with no retinopathy and urine albumin excretion <30 mg/24 h composed the primary prevention group and 55 patients with mild retinopathy and albumin excretion<300 mg/24 h comprised the secondary intervention group. All subjects were then randomized to intensive

(>2 insulin injections per day) or conventional (1–2 insulin injections per day) therapy. The goal of the conventional group was the absence of symptomatic hyper- or hypoglycemia. The numeric targets for the intensive group were fasting glucose <140 mg/dl, 2 h postprandial glucose <200 mg/dl, and HbA1c <7%. Follow-up data were obtained at 3 months and then every 6 months for 6 years. Separation of HbA1c (9.4% in the conventional subjects and 7.1% in those receiving intensive treatment) was maintained through the study. Risk reduction for progression of retinopathy in the combined cohorts was 69%, a result similar to the DCCT (see Table 39.1). Intensive therapy also reduced the average risk of worsening in retinopathy by 70%. After 6 years, nerve conduction velocities were significantly improved in the intensively treated subjects while median nerve conduction velocities deteriorated in the subjects receiving conventional therapy. Intensive glycemic control by MDI delayed the onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy compared to conventional treatment. This study extended the confirmation of beneficial effects of intensive glycemic therapy seen in the DCCT and in the SDIS to individuals with type 2 diabetes.

Table 39.1 Risk reductions in microvascular disease

Study	Retinopathy		Microalbuminuria	
	Primary (%)	Secondary (%)	Primary (%)	Secondary (%)
DCCT	76	54	34	43
Kumamoto	76	56	62	52

The DCCT was designed as an intervention trial to compare two treatment modalities and not to determine complication risk at various levels of glycemic control. Nonetheless, the data were analyzed and presented in a subsequent paper, which examined the relationship between glycemic levels, as reflected by HbA1c, and the risk of retinopathy progression.[22] There was a continuously increasing risk of retinopathy progression with increasing mean HbA1c levels. Some prior retrospective studies had not found such a relationship for microalbuminuria[23] and retinopathy progression[24] for HbA1c levels below 8%. Analysis of the DCCT data, comprising over 9000 patient-years of observation, found a similar and significant reduction in retinal, renal, and neurological complication rates associated with decline in HbA1c. This relationship was consistent over the entire range of HbA1c in the study, even for levels less than 8% (see Fig. 39.1). Thus for a 10% reduction in HbA1c there is a constant

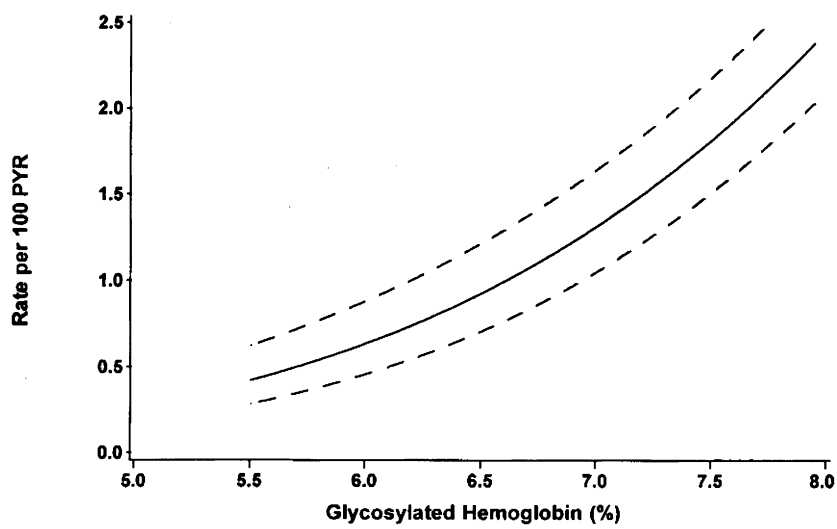

Fig. 39.1 The absolute risk of sustained retinopathy progression (hazard rate per 100 patient-years) in the combined treatment groups as a function of the updated mean HbA1c during follow-up in the DCCT estimated from a Poisson progression model with 95% confidence bands (from DCCT Research Group[25], with permission)

39% decrease in retinopathy progression. As the rate of events per 100 patient-years is greater at higher HbA1c values, the absolute reduction in risk is greater with reduction in HbA1c at higher values. Nonetheless, there exists no threshold HbA1c value below which a reduction in HbA1c is not accompanied by a reduction in risk for retinopathy and for nephropathy. When the risk of progression of retinopathy is extrapolated over the 9 years of follow-up in the DCCT the cumulative incidence of progression is lowered from 20% at a HbA1c of 8% to an incidence of 5.5% at a HbA1c of 6%.[25]

Another question regarding the extrapolation of the DCCT, SDIS, and Kumamoto studies was whether the motivated volunteers screened and selected for enrollment were representative of the general diabetes patient population. In order to address the comparability of the DCCT cohort and the validity of generalizing the DCCT results, a contemporaneous population based cohort was necessary. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was a large population based incidence study of people with both type 1 and type 2 diabetes conducted concurrently with the DCCT.[26] The measurement of the main endpoint, diabetic retinopathy, was determined using similar methods of classification. Of the patients with type 1 diabetes being followed in the WESDR, 891 subjects underwent baseline and 4-year follow-up assessment. Of these, 39 and 111 met the DCCT inclusion criteria for the primary and secondary cohorts, respectively. The DCCT study cohorts were comparable to the WESDR type 1 population with regard to age, gender, BMI, blood pressure, and insulin dose. Because of the DCCT baseline eligibility criteria, retinopathy severity was higher in the WESDR group. Thus, the comparison supports the extrapolation of the DCCT results to the general type 1 diabetes population.

At the close of the DCCT in 1993, subjects who were in the conventional group were offered intensive treatment and as part of the study closeout were instructed in intensive therapy. Those subjects in both the former intensive and conventional groups were also offered participation in an observational study to continue following the DCCT cohorts. The Epidemiology of Diabetes Intervention and Complications (EDIC) is a follow-up observational study of the DCCT cohort to continue to monitor the long-term micro- and macrovascular complications of type 1 diabetes.[27] One of the study objectives is to compare the effects of the prior intensive or conventional treatments administered during the DCCT on the subsequent development and progression of more advanced retinopathy and nephropathy. About 1375 of the 1421 surviving DCCT subjects participated in the EDIC study. During the study all subjects received their diabetes care from their own physicians but were seen yearly for evaluation by the research team. Annual retinal fundus photography was obtained based on year of enrollment in the DCCT, with 1208 (605 in the intensive DCCT group) subjects undergoing evaluation at year 4 of EDIC.

By the end of the first year of EDIC, the HbA1c levels in the 1208 subjects had begun to merge (8.1% in the conventional and 7.7% in the intensive group). During the first 4 years of EDIC, the median HbA1c values were 8.2% for the conventional and 7.9% for the former intensive groups; a smaller but still statistically significant difference. The year-4 fundus photography results revealed that 49% of the subjects from the conventional group had progression of retinopathy from the DCCT baseline, while only 18% of the intensive group had progression. To assess the change in retinopathy during the EDIC years, the level of retinopathy was evaluated for fundus photographs obtained at years 1–4 of EDIC and retinopathy progression was compared to the level of retinopathy at the end of the DCCT (see Fig. 39.2). By EDIC year 4 the cumulative incidence of further progression of retinopathy was 70% lower in the intensive than in the conventional treatment group.[28] The significant reduction in retinopathy from end of the DCCT to year 4 of EDIC was similar regardless of the level of retinopathy at the end of the DCCT. Severe nonproliferative retinopathy, or worse, occurred in 10% of the conventional group but only 2% of the intensive group. This 76% reduction was significant even when adjusting for the level of retinopathy at the end of the DCCT. In addition, the risk of progression of retinopathy was highly associated with the mean HbA1c level during both the DCCT and EDIC studies.

Similar results were detected for progression of nephropathy during EDIC. At years 3 and 4, the onset of microalbuminuria was reduced 53%, from 11% in the conventional treatment group to 5% in the intensive group. The risk of new albuminuria was decreased by 86% in the intensive group.

Fundus photography and urine albumin measurements continued to be collected throughout the EDIC study. Despite statistically nonsignificant Hb1Ac differences between the former intensive and conventional groups by year 5 of EDIC, the cumulative incidence of further 3-step progression of retinopathy as well as development of

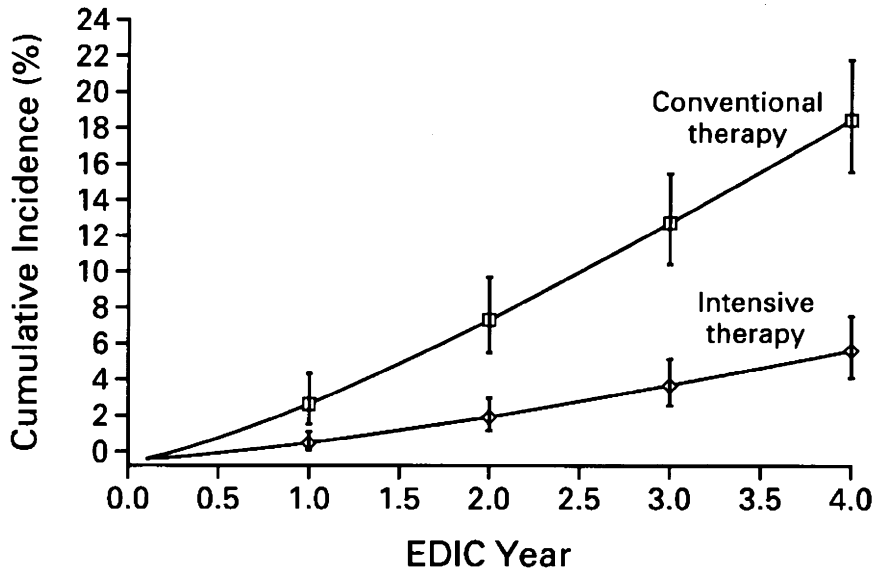

Fig. 39.2 Cumulative incidence of further progression of retinopathy (an increase of at least three steps from the level at the end of the DCCT) in the former conventional therapy and intensive therapy groups. The data are based on regression analysis adjusted for the level of retinopathy at the end of the DCCT, whether patients received therapy as primary prevention or secondary intervention, and both the duration of diabetes and the glycosylated hemoglobin value on enrollment in the DCCT. Patients who underwent scatter photocoagulation during the DCCT were excluded from the analysis (22 in the conventional group and 9 in the intensive therapy group). Bars denote 95% confidence intervals (from DCCT/EDIC Research Group[28], with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved)

microalbuminuria and albuminuria at EDIC year 8 continued to be less in the former DCCT intensive treatment group.[29,30]

During the 8 years of EDIC, with an increase in the HbA1c of the intensive group and a reduction in the separation of HbA1c levels between the intensive and conventional DCCT groups, it would be expected, based on the relationship of glycemic control to microvascular disease,[22] that the effects of intensive therapy during the DCCT would be reduced. In contrast, the benefits of intensive control on retinopathy and on nephropathy persist for at least 8 years after termination of separate intensive and conventional treatment and despite rising HbA1c levels. The positive effects of glycemic control appear to be long lasting. These results could be attributed to the effects of chronic hyperglycemia on advanced glycation end products accumulation in end organs, leading to microvascular disease,[31] but the exact reason for the persistence of the effects of past glycemic exposure is not known.

Thus, intensive glycemic control will delay the onset and slow the progression of diabetic microvascular disease in individuals with both type 1 and in type 2 diabetes. From the DCCT and EDIC study results, the positive benefits of intensive over conventional therapy will be greater the earlier they are implemented and can persist for up to 8 years after cessation of intensive treatment.

Macrovascular Disease

Although microvascular disease can lead to substantial morbidity, the major cause of mortality in both type 1 and type 2 diabetes is cardiovascular disease.[32–35] As was the case with microvascular disease, clinicians had long recognized an association of poor glycemic control with the development of macrovascular outcomes in patients with diabetes. Several prospective studies have confirmed that hyperglycemia is a predictor for cardiovascular

disease.[36–39] Nonetheless, the belief that reduction of hyperglycemia decreases cardiovascular disease is not universally accepted.[40,41]

In the DCCT, the number of combined major macrovascular events (cardiac, cerebrovascular, and peripheral vascular) was twice as high in the conventional treatment (40 events) group than in the intensive treatment group (23 events), but this difference was not statistically significant.[42] Lipid risk factors associated with cardiovascular disease such as increased total and LDL cholesterol and elevated triglyceride levels were all significantly reduced in the intensive treatment group. As mentioned above, the DCCT cohorts were of young age at entry (13–39 years). In addition, the inclusion criteria eliminated patients with hypertension, hypercholesterolemia, and known cardiovascular disease. Such baseline demographics made it likely that few cardiovascular events would occur by DCCT study end.

One of the objectives of the EDIC study was to continue to monitor CV outcomes in the DCCT cohort. In addition, surrogate measures of cardiovascular disease were added to the microvascular assessments. B-mode ultrasonography was used to measure carotid intima-media wall thickness (IMT), an established index of atherosclerosis,[43] at years 1 and 6 of EDIC.[44] Increased IMT was significantly associated with HbA1c both at the time of measurement and during the 6.5 years of the DCCT. Subjects receiving conventional treatment during the DCCT developed greater age related increases in IMT than the intensively treated subjects.

The DDCT/EDIC Research Group had decided in 1996 not to perform any between treatment group analyses of cardiovascular events until a set target of 50 participants in the DCCT conventional group had experienced a CV event. This would ensure 85% power to detect a 50% reduction in the risk of CV events between the DCCT intensive and conventional treatment groups. Cardiovascular events were nonfatal myocardial infarction; nonfatal stroke; death judged to be due to CV disease; subclinical myocardial infarction (identified on annual EKG); angina; or the need for revascularization with angioplasty or coronary-artery bypass. The target number of conventional group participants was reached at the beginning of 2005 and the analyzed results were announced in June of that year. Among the 1375 DCCT/EDIC participants who remained in the study at the time of analysis, those in the former intensive treatment group had a 42% decrease (95% confidence interval, 9–63%; $p = 0.02$) in the risk of any CV disease and a 57% reduction (95% confidence interval 12–79%; $p = 0.02$) in the risk of nonfatal myocardial infarction or stroke or death from CV disease.[45] The mean HbA1c during the DCCT accounted for most of the effects of intensive treatment on reducing the risk of cardiovascular disease. This study was the first to show that intensive insulin therapy reduces the incidence of cardiovascular disease in individuals with diabetes.

Several studies looked at the effect of glycemic control on cardiovascular disease in type 2 diabetes. As mentioned above, the Kumamoto study evaluated a cohort of 110 individuals with type 2 diabetes. The total number of combined cardiovascular events in the conventional treatment group was twice that of the intensive treatment group, but was not statistically significant due to the small number of patients in the trial.

A much larger group of patients were studied in the United Kingdom Prospective Diabetes Study. The UKPDS was a multicenter intervention trial of over 5000 patients with newly diagnosed type 2 diabetes. The objective of the UKPDS was to determine if intensive glycemic control reduces the risk of diabetic complications in individuals with type 2 diabetes and, as a secondary aim, to compare various treatment modalities.[46] The study was conducted by general practitioners in 23 centers throughout the UK between 1977 and 1991. Patients with type 2 diabetes, 25–65 years of age, with FBG >6 mmol/L on two occasions were enrolled. All subjects were initially treated with diet modification alone for a 3-month period. At the end of 3 months, those patients who failed to achieve glycemic control (FBG >6.0 mmol/L) were randomized to various pharmacologic treatment modalities. Patients with BMI over 120% ($N = 2187$) were randomized to diet alone, sulfonylurea (SU) agent (chlopropamide or glibenclamide), insulin, or metformin. Non-overweight patients ($N = 2022$) were randomly assigned to diet alone, sulfonylurea therapy (chlorpropramide or glibenclamide/glipizide) or insulin.

The conventional or diet alone subjects received dietary education every 3 months with goals to attain normal body weight, eliminate hyperglycemic symptoms, and maintain HbA1c levels <15 mmol/L. If either symptoms of hyperglycemia or FBG > 15 mmol/L occurred then the subject was again randomized to one of the pharmacologic agents with the aim once more to avoid hyperglycemic symptoms and keep FBG <15 mmol/L. The goal of intensive therapy was to attain near-normal FBG values (<6 mmol/L). As with the conventional cohort, a second drug was added if the FBG exceeded 15 mmol/L. Median follow-up was 10.7 years.

Unlike the DCCT, SDIS, and Kumamoto studies, the level of glycemia and HbA1c in the diet and pharmacologic groups was not maintained throughout the trial. Addition of drugs to the initial designated monotherapy was often necessary. HbA1c levels increased in all groups over the duration of the study so that, at the end of 10 years, the intensive treatment group median HbA1c level was 7.0% as compared to a 7.9% value for the conventional treatment group. Despite this modest difference, intensive glycemic control with either sulfonylurea or insulin resulted in a significant 21% risk reduction in the progression of retinopathy and a 33% risk reduction in albuminuria.[46] There was no evidence of any glycemic threshold for the effects of intensive glucose control on reducing microvascular complication rates. Thus the results of the UKPDS reaffirm the positive effect of intensive glucose therapy with insulin (and/or sulfonylurea) on reducing the development of microvascular complications in persons with type 2 diabetes.

The results for macrovascular endpoints in the UKPDS were not as definitive. The 16% risk reduction for combined fatal or nonfatal myocardial infarction and sudden death was just above statistical significance ($p = 0.052$). Epidemiologic analysis, however, revealed a continuous association between the risk of cardiovascular complications and the level of glycemia.[47] When overweight subjects treated with metformin were compared to the conventional diet-treated overweight group, there were significant risk reductions for diabetes-related death and diabetes-related endpoint, including fatal or nonfatal myocardial infarction.[48] These results occurred with only a 0.6% HbA1c separation between intensive (7.4%) and conventional (8%) groups, suggesting that the beneficial effects of metformin could have also been due to the drug's ability to improve lipid levels and decrease levels of plasminogen-activator inhibitor type 1. In contrast to the findings with metformin alone, there appeared to be an increase in diabetes-related death when metformin was added to SU to improve glycemic control. Explanations for these disparate results are lacking and a definitive conclusion regarding the effect of intensive glycemic control on CV outcomes based on the UKPDS study results cannot be reached.

In a later study, the effects of intensive glycemic control were evaluated in patients admitted to the coronary care units of 19 Swedish hospitals with suspected acute myocardial infarction and hyperglycemia (admission glucose levels at or above 198 mg/dl). In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study,[49] 620 patients were randomized to a control or infusion group. Those 306 patients in the infusion group received intravenous insulin infusion while in the coronary care unit (CCU) followed by four times daily subcutaneous insulin for 3 or more months to maintain glucose levels in a stable normoglycemic range. The control group of 314 patients was treated according to standard CCU practice and did not receive insulin unless clinically indicated. The primary aim of the DIGAMI study was to test whether early and rapid metabolic control in diabetic patients with acute myocardial infarction would reduce 3-month mortality rate. At 3 months, although HbA1c was $7.5 \pm 1.8\%$ in the control group and $7.0 \pm 1.6\%$ in the infusion group, the mortality rates were not significantly different. At 1 year, HbA1c levels in the infusion were lower than in the control group (7.0% vs. 7.5%). There was also a 31% lower 1-year mortality rate in the infusion group (18.6% vs. 26.1%, $p = 0.0273$). A larger study of 1253 patients (DIGAMI 2)[50] was designed to discern whether the insulin infusion alone or the combination of insulin infusion followed by intensive subcutaneous insulin administration was responsible for the reduced 1-year mortality rates seen in the initial DIGAMI study. Unfortunately, the study not only was unable to answer this question but also was unable to replicate the initial DIGAMI reduction in mortality rates, as the HbA1c levels in all groups were essentially identical (approximately 6.8%).

A smaller earlier intervention trial of 153 male subjects with type 2 diabetes also evaluated intensive versus conventional glycemic control. The Veterans Affairs Cooperative Study in Glycemia Control was a feasibility study for a larger trial.[51] Subjects were randomized to intensive therapy, using a stepped multiple insulin injection algorithm plus glipizide, or conventional treatment, using 1 or 2 insulin injections a day. The two groups achieved a HbA1c difference of 2.1% (9.2% vs. 7.1%) for 27 (range 18–35) months. The percentage of subjects experiencing a cardiovascular (CV) event was higher, though not statistically so, in the intensive (21.3%) than in the conventional group (11.5%).

The large clinical trials showing beneficial effects of intensive therapy on microvascular disease in individuals with type 2 diabetes fail to show a consistent statistically significant benefit on macrovascular disease. In the case of the UKPDS, the largest of the trials, the fact that patients were selected for the presence of newly diagnosed diabetes and for the absence of known CV disease could have resulted in the inability of the study to reach a significant difference in myocardial infarction rates. In addition, the continually rising glucose levels during

the study, resulting in both an intensive group HbA1c above 8.0% and a modest HbA1c separation during the last 5 years of the trial, may have contributed to the lack of significant reduction in CV disease. It has long been recognized that an increase in CV risk occurs prior to the development of overt type 2 diabetes, at a time when HbA1c may be within the normal range and impaired glucose intolerance is present.[52–54] Much of this increased risk may be related to the lipid, blood pressure, and other metabolic abnormalities that often occur in individuals with impaired glucose tolerance. On the other hand, the ability of intensive glycemic control to decrease CV disease may require achieving lower glucose levels than those resulting in improvement in microvascular complications.

In order to determine whether achieving such lower glucose levels would indeed result in a reduction in CV events in individuals with type 2 diabetes mellitus, the NIH has sponsored the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial.[55] Over 10,000 middle-aged and older patients with type 2 diabetes at high risk for CV disease were randomized into the ACCORD trial at 77 centers in the United States and Canada. The ACCORD study is also, using a double 2×2 factorial design, evaluating the effects on CV events of treatment to increase high-density lipoprotein cholesterol and lower triglyceride (in the context of optimal LDL cholesterol and good glycemic control) and of intensive blood pressure control (in the context of good glycemic control). Primary outcome is the first occurrence of a major CV event, defined as nonfatal MI, nonfatal stroke, or cardiovascular death. The glycemic arm of the trial tests whether a therapeutic strategy that targets a HbA1c level of <6.0% will reduce the occurrence of major CV events more than a strategy that targets a HbA1c in the 7.0–7.9% range. The ACCORD trial is scheduled to conclude on June 30th, 2009, at which time the participants will have been followed for 4–8 (mean 5.6) years.

In summary, based on currently completed clinical trials, intensive glycemic therapy will reduce the incidence of cardiovascular disease and events in individuals with type 1 diabetes. Whether intensive glycemic control has the same effect in type 2 diabetes remains to be proven. It is important to keep in mind that control of blood pressure and correction of lipid abnormalities will result in substantial reductions in cardiovascular disease in individuals with type 2 diabetes[56–58] and such therapy should be instituted.

Adverse Effects of Intensive Glycemic Control

Intensive glycemic control is not without possible side effects. These include weight gain, drug-specific side effects, costs in both time and money, and hypoglycemia. The occurrence of low blood glucose level carries the greatest risk, including significant morbidity and death. Several fold increases in mild to moderate hypoglycemia occur in all trials utilizing intensive glycemic control.[59] In the DCCT, the incidence of severe hypoglycemia (documented BG <50 mg/dl requiring the assistance of another person for correction) was increased threefold in the intensive treatment group (61.2 episodes/100 patient-years) compared to the conventional group (18.7 episodes/100 patient-years).[60] The intensive group did not have an increase in deaths, myocardial infarctions, or strokes attributable to hypoglycemia. There was also no difference in cognitive function, as assessed by a battery of cognitive testing, in the intensive treatment group at the close of the DCCT[61] or at follow-up testing 18 years from the onset of the study.[62] Similar results regarding the incidence of hypoglycemia were found in the Stockholm Diabetes Intervention Study. The incidence of hypoglycemia, including recurrent episodes, during the DCCT was found to have greater association with the most recent HbA1c than with past values or the average HbA1c during the DCCT trial.[25] There was a 26% (95% CI 22–29) increase in the risk of severe hypoglycemia for each 10% reduction in current HbA1c in the intensive group. The increased risk per 10% lower HbA1c was 54% (95% CI 49–60) in the conventionally treated subjects. For both treatment groups, the risk gradient for HbA1c <8% was lower than for values >8%.[25] Over the 6.5 years of the DCCT, 65% of the patients in the intensive group had at least one episode of severe hypoglycemia vs. 35% of the conventionally treated subjects. The number of prior episodes of hypoglycemia was the strongest predictor of future episodes.[60]

In type 2 diabetes, the risk of hypoglycemia and severe hypoglycemia is an order of magnitude less than that in type 1 diabetes. In the UKPDS, the rate of hypoglycemic episodes increases over time in the insulin treated patients but decreases over time in patients treated with oral agents. The percentage of patients with any

hypoglycemia was 15.2% for patients on chlorpropramide, for glibenclamide – 20.5%, for insulin – 25.5%, for metformin – 8.3%, and for diet alone – 7.9%. Severe hypoglycemic episodes occurred in 1.8–2% of patients on insulin, 1.0–1.4% on glibenclamide, 1–1.2% on chlorpropramide, 0.6% on metformin and 0.7% on diet alone.[46,48]

Intensive glycemic control also lowers the threshold for hormonal response to hypoglycemia, leading to impaired glucose counter-regulation.[63,64] Patients with type 2 diabetes release counter-regulatory hormones at a higher plasma glucose level and in higher amounts for a similar degree of overall glycemic control.[65] This may account for the lower incidence of hypoglycemia in type 2 diabetes.

Weight gain will also accompany intensive glycemic control, with the exception of patients treated with metformin. In the DCCT, after 6.5 years, the prevalence of being overweight (BMI >27.8 kg/m^2 for men and >27.3 kg/m^2 for women) was 33.1% in the intensive treatment group compared to 19.1% in the conventional treatment group.[66,67] Intensive group subjects with a family history of type 2 diabetes experienced greater central weight gain than subjects with no such family history.[68] Weight gain is especially troubling in individuals with type 2 diabetes, given the high incidence of associated obesity. In the UKPDS, subjects treated with SUs gained 1.7 and 2.6 kg, while patients on insulin gained an average of 4.0 kg.[46]

Side effects, besides hypoglycemia and weight gain, of the oral agents used to achieve glycemic control in individuals with type 2 diabetes include gastrointestinal symptoms, lactic acidosis, edema, and fluid retention and, in the case of the thiazolidenedione class, congestive heart failure and possible increase in myocardial infarction rates.[69–71] The possible adverse effects of high insulin levels in the setting of insulin resistance on vascular smooth muscle cell migration/proliferation and the development of atherosclerosis remain controversial.[72,73]

Glycemic Control Target Levels

Hemoglobin A1c levels are used as a measurement to both determine recent mean plasma glucose levels and to predict future risk of developing diabetes complications. Recently, the concept of glucose variability, particularly postprandial glucose levels, as an additional independent predictor of complications has been proposed.

Several epidemiological studies have shown that plasma glucose levels 2 h after an oral glucose challenge is an independent predictor of cardiovascular disease risk.[74–76] Post-challenge absolute and incremental glucose levels were more strongly associated with B-mode ultrasonography carotid artery intima–media thickness than fasting glucose levels or HbA1c.[77] The majority of the patients in these studies, however, had impaired glucose tolerance(IGT) or mild diabetes and HbA1c levels that were within the nondiabetic reference ranges.

The effect of postprandial glucose lowering agents on macrovascular disease has been looked at in interventional studies of individuals with IGT and type 2 diabetes. The STOP-NIDDM research study[78] evaluated whether the alpha-glucosidase inhibitor acarbose, a compound that specifically reduces postprandial hyperglycemia, would reduce the risk of progression to diabetes, development of hypertension, and cardiovascular disease. In this international, multicenter placebo-controlled trial, 1429 patients with impaired glucose tolerance were randomized to placebo or acarbose and followed for a mean of 3.3 years. Acarbose use was associated with a 49% relative risk reduction in CVD events (hazard ratio of 0.51; 95% confidence interval 0.28–0.95, $p = 0.03$). Esposito et al.[79] compared the effects of the insulin secretagogues repaglinide and glyburide in 175 patients with type 2 diabetes. Following a 6–8 week titration period, subjects were randomized to one of the two medications for 12 months. Carotid B-mode ultrasound intima–media thickness (CIMT) measurements and serum samples for inflammatory markers were obtained at baseline and at study end. Despite similar declines in HbA1c levels of approximately 0.9%, postprandial glucose was 148 $\pm$ 28 mg/dl in the repaglinide group and 180 $\pm$ 32 mg/dl in the glyburide group ($p < 0.01$). CIMT regression was observed in 52% of patients in the repaglinide group but only 18% of the patients receiving glyburide ($p < 0.01$). Inerleukin-6 and c-reactive protein also decreased more in the repaglinide group ($p = 0.04$ and 0.02, respectively).

Proposed mechanisms through which postprandial hyperglycemia may impact endothelial function include increased production of inflammatory markers and free radicals.[80] Monier et al.[81] assessed the relative contributions of sustained hyperglycemia and acute glucose fluctuations on measures of oxidative stress in 21 patients

with type 2 diabetes and 21 age and sex matched controls. Urinary 8-iso prostaglandin F 2 alpha, an indicator of total body free radical production, was associated with both the mean amplitude of glycemic excursions (MAGE) ($r = 0.86$, $p < 0.001$) and postprandial incremental area under the curve ($r = 0.55$, $p < 0.009$). There was no significant correlation between free radical production and 24 h glucose production, fasting glucose concentration, or HbA1c.

Despite the correlations of surrogate measures of atherosclerosis with postprandial glucose elevations seen in the above small studies, there has been no confirmatory evidence from the large clinical trials of an independent effect of glycemic variability on complications of diabetes. Several analyses of the DCCT data set have found that glycemic variability does not independently predict the risk of complications beyond that of HbA1c level.[82–84] In 2001, an ADA consensus panel did not recommend the routine use of postprandial blood glucose testing.[85]

Clinical target levels for intensive glycemic control are based on consensus committees reviewing the available study data. Unfortunately, as presented in the sections above, none of the large randomized trials evaluating the effects of glycemic control on micro and macrovascular complications have attained mean HbA1c levels in the nondiabetes range. Thus, a difference of opinion exists among diabetologists and professional organizations regarding specific glycemic targets, with no hard evidence supporting one over the other. The two most cited glycemic target levels from United States organizations are the American Diabetes Association (ADA) recommendations[86] and the American Association of Clinical Endocrinologists (AACE) Medical Guidelines.[87]

Clearly, patients with both type 1 and type 2 diabetes must be given appropriate dietary and pharmacologic therapy to eliminate the symptoms of hyperglycemia and prevent the consequences of extreme uncontrolled diabetes, i.e., ketoacidosis and hyperosmotic state. The positive effects of intensive glycemic control on the development and the progression of microvascular disease in the clinical trials of patients with both type 1 and type 2 diabetes form the basis for the ADA target glucose and HbA1c levels as outlined in Table 39.2 below. A case could be made to attempt to achieve glucose levels as close to normal as possible as, in secondary clinical trial analyses, there is no threshold of HbA1c level below which further reduction in microvascular disease does not occur. Thus, the AACE glycemic HbA1c target of less than 6.5% is lower than that of the ADA.

Table 39.2 Recommended glycemic goals

	Nondiabetes glycemic levels	Diabetes treatment targets
A1C	<6	<7
FBG (plasma)	<100 mg/dl	70–130 mg/dl
	<5.6 mmol/l	3.9–7.2 mmol/l
2 h	<140 mg/dl	<180 mg/dl
postmeal BG (plasma)	<7.8 mmol/l	<10 mmol/l

Source: Data from American Diabetes Association.[86]

Concurrent chronic illness does not limit the achievement of glycemic control.[88] This must be tempered by the fact that the incidence of hypoglycemia will be increased threefold for near-normal glucose levels. For individuals with other diseases where the consequences of severe hypoglycemia may result in morbidity or death, the attainment of normal glucose levels with insulin or SU therapy would not be advisable. If the patient has a disease which significantly shortens life expectancy, then the need to prevent long-term complications is absent. Treatment goals must be individualized to account for concomitant disease, the presence of hypoglycemic awareness, and the ability of the patient to monitor glucose levels and follow an intensive treatment plan. For patients with type 2 diabetes, it is also important to focus on the concomitant dysmetabolic state and to address any abnormalities in lipids and blood pressure. The ultimate goal of glycemic control is to attain the lowest HbA1c level that will not adversely affect patient safety. Although the recommended goal is a HbA1c <7% or <6.5%, for most patients without other medical illnesses one can attempt to reach a value of 6.0%, providing no treatment side effects occur. For patients with mild or early onset diabetes, on diet alone or on pharmacologic agents that cannot cause hypoglycemia, HbA1c levels within the normal range should be readily achievable.

Summary

Intensive glycemic control effectively prevents the occurrence and delays the progression of microvascular complications in both type 1 and type 2 diabetes. Intensive therapy will also reduce the incidence of cardiovascular disease in type 1 diabetes. Demonstration of beneficial effects of glycemic control on decreasing CV events in type 2 diabetes is lacking. Attention to blood pressure and lipid control is also important in both types of diabetes.[89] The incidence of hypoglycemia is increased threefold with intensive glycemic control. Current recommendations advocate attaining near-normal glucose levels when safely feasible.

Helpful internet source for additional information on glycemic goals:

- ADA clinical practice guidelines (http://www.diabetes.org/diabetescare)

References

1. Engerman R, Bloodworth JM, et al. Relationship of microvascular disease in diabetes to metabolic control. *Diabetes*. 1977;26:760–769.
2. Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. *Diabetes*. 1987;36: 808–812.
3. Cohen AJ, McGill PD, Rosetti RG, Guberski DL, Like AA. Glomerulopathy in spontaneously diabetic rat: impact of glycemic control. *Diabetes*. 1987;36:944–951.
4. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care*. 1978;38:252–261.
5. Ingelfinger FJ. Debates in diabetes. *N Engl J Med*. 1977;296:1228–1230.
6. Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. *N Engl J Med*. 1984;311:365–372.
7. Dahl-Jorgensen K, Hanssen KF, Kierulf P, Bjoro T, Sandvik L, Aagenaes O. Reduction of urinary albumin excretion after 4 years of continuous subcutaneous insulin-infusion in insulin-dependent diabetes mellitus. *Acta Endocrinologica*. 1988;117:19–25.
8. Lauritzen T, Frost-Larsen K, Larsen H-W, Deckert T. Steno Study Group. Effect of 1 year of near- normal blood glucose levels on retinopathy in insulin- dependent diabetes. *Lancet*. 1983;1:200–204.
9. DCCT 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.
10. DCCT Research Group. The effects of intensive treatment of diabetes therapy on the development and progression of neuropathy. *Ann Int Med*. 1995;122:561–568.
11. DCCT Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the DCCT. *Diabetologia*. 1998;41:416–423.
12. Reichard P, Nilsson BY, Rosenquist U. The effect of long term intensified treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med*. 1993;329:304–309.
13. Implications of the Diabetes Control and Complications Trial. American Diabetes Association Position Statement. *Diabetes Spectrum*. 1993;6:225–227.
14. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA*. 1988;260:2864–2871.
15. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: X. Four year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Opthalmol*. 1989;107:244–249.
16. Lasker RD. DCCT: implications for policy and practice. *N Engl J Med*. 1993;329:1035–1036.
17. Nathan DM. Inferences and implications. Do results from the DCCT apply in NIDDM? *Diabetes Care*. 1995;18:251–257.
18. Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev*. 1995;75:473–486.
19. Balkau B, Eschwege E, Papoz L, et al. Risk factors for early death in non-insulin-dependent diabetes and men with known glucose tolerance status. *Br Med J*. 1993;307:295–298.
20. Hsueh WA, Law RE. Cardiovascular risk continuum: implications of insulin resistance and diabetes. *Am J Med*. 1998;105(1A):4S-14S.
21. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus. *Diab Res Clin Prac*. 1995;28:103–117.

22. DCCT Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the DCCT. *Diabetes*. 1995;44:968–983.
23. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria inpatients with insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;332:1251–1255.
24. Warram JH, Manson JE, Krolewski AS. Glycosylated hemoglobin and the risk of retinopathy in insulin-dependent diabetes. *N Engl J Med*. 1995;332:1305–1306.
25. DCCT Research Group. The absence of a glycemic threshold for the development of long- term complications: The perspective of the DCCT. *Diabetes*. 1996;45:1289–1298.
26. DCCT Research Group, Klein R, Moss S. A comparison of the study populations in the DCCT and the WESDR. *Arch Int Med*. 1995;155:745–754.
27. EDIC Research Group. EDIC: design, implementation and preliminary results of a long-term follow-up of the DCCT cohort. *Diabetes Care*. 1999;22:99–111.
28. DCCT/EDIC Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381–389.
29. DCCT/EDIC Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes. *JAMA*. 2002;287:2563–2569.
30. DCCT/EDIC Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy. *JAMA*. 2003;290:2159–2167.
31. Genuth S, Sun W, Cleary P, et al. Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Intervention and Complications participants with type 1 diabetes. *Diabetes*. 2005;54: 3103–3111.
32. Geiss S, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Harris M, ed. *Diabetes in America*. 2nd ed. Bethesda, MD: National Institutes of Health (NIH publ.No 95-1468); 1995:133–155.
33. Krolewski AS, Kosinski EJ, Warram JH, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol*. 1987;59:750–755.
34. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia*. 2003;46:760–765.
35. Thom T, Haase N, Rosamond W, et al. for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 113: e85–e151; 2006
36. Niskanen L, Turpeinen A, Pentilla I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15 year follow-up from the time of diagnosis. *Diabetes Care*. 1998;21: 1861–1869.
37. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all cause and cardiovascular mortality. The San Antonio Heart Study. *Diabetes Care*. 1998;21:1167–1172.
38. Lehto S, Ronnemma T, Pyorala K, Laakso M. Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. *Arterioscler Thromb Vasc Biol*. 1999;19:1014–1019.
39. Selvin E, Marinopoulos S, Berkenblit G, et al. Met-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Int Med*. 2004;141:421–431.
40. Barrett-Connor E. Does hyperglycemia really cause coronary heart disease? *Diabetes Care*. 1997;20:1620–1622.
41. Orchard TJ, Olson JC, Erbey JR, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10 year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*. 2003;26:1374–1379.
42. DCCT Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the DCCT. *Am J Cardiol*. 1995;75:894–903.
43. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 1995;26:386–391.
44. DCCT/EDIC Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294–2303.
45. DCCT/EDIC Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;355:2643–2652.
46. UKPDS Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
47. Stratton IM, Adler AI, Neil HA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*. 2000;321:405–412.
48. UKPDS Group. Effect of intensive blood glucose control with metformin complications on in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.
49. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57–65.

50. Malmberg K, Ryden L, Wedel H, et al. for the DIGAMI 2 investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26:650–661.
51. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the veterans affairs diabetes feasibility trial. *Arch Int Med*. 1997;157:181–188.
52. Balkau B, Shipley M, Jarrett RJ, Pyorala M, Forhan A, Eschwege E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20 year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care*. 1998;21:360–367.
53. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a meta-regression analysis of published data form 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233–240.
54. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Int Med*. 2004;141: 413–420.
55. The ACCORD Study Group. Action to control cardiovascular risk in diabetes (ACCORD) trial: design and methods. *Am J Cardiol*. 2007;99:21i-33i.
56. Bakris GL. The importance of blood pressure control in the patient with diabetes. *Am J Med*. 2004;116(S5A):S30–S38.
57. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
58. Colhoun HM, Betteridge DJ, Durrington PM, et al. for the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multi-centre randomized placebo-controlled trial. *Lancet*. 2004;364:685–696.
59. Cryer P. Hypoglycemia: the rate limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia*. 2002;456:937–948.
60. DCCT Research Group. Hypoglycemia in the DCCT. *Diabetes*. 1997;46:271–286.
61. DCCT Research Group. Effects of intensive diabetes therapy in neuropsychological function in adults in the DCCT. *Ann Int Med*. 1996;124:379–388.
62. Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med*. 2007;356:1842–1852.
63. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS. Defective glucose counteregulation after strict glycemic control of insulin-independent diabetes mellitus. *N Engl J Med*. 1987;316:1376–1383.
64. Kinsley BT, Windom B, Simonson DS. Differential regulation of counter-regulatory hormone secretion and symptoms during hypoglycemia in IDDM. *Diabetes Care*. 1995;18:17–26.
65. Levy CJ, Kinsley BT, Bajaj M, Simonson DS. Effect of glycemic control on glucose counter-regulation during hypoglycemia in NIDDM. *Diabetes Care*. 1998;21:1330–1338.
66. DCCT Research Group. Adverse events and their association with treatment regimens in the diabetes control and complications trial. *Diabetes Care*. 1995;18:1415–1427.
67. DCCT Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the diabetes control and complications trial. *Diabetes Care*. 2001;24:1711–1721.
68. Purnell JQ, Dev RK, Steffes MW, et al. Relationship of family history of type 2 diabetes, hypoglycemia and autoantibodies to weight gain and lipids with intensive and conventional therapy in the diabetes control and complications trial. *Diabetes*. 2003;52:2623–2629.
69. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med*. 1999;131:281–303.
70. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2425–2471.
71. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. *Diabetes Care*. 2007;30:2148–2153 May 29, 2007 Epub.
72. Abraira C, Maki KC. Does insulin treatment increase cardiovascular risk in NIDDM? *Clin Diabetes*. 1995;13:29–31.
73. Nigro J, Osman N, Dart AM, Little PJ. Insulin resistance and atherosclerosis. *Endocrine Rev*. 2006;27:242–259.
74. The DECODE Study Group, the European Diabetes Epidemiology Group. Glucose intolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999;354:617–621.
75. Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care*. 1998;22:360–367.
76. Hanefeld M, Fischer S, Julius U, et al. the DIS Group. Risk factors for myocardial infarction and death in newly detected NIDDM: the diabetes intervention study, 11 year follow-up. *Diabetologia*. 1996;39:1577–1583.
77. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fueker K, Hanefeld M. Post challenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care*. 2000;23:1830–1834.
78. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laasko M. The Stop NIDDM Trial. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA*. 2003;290:486–494.

79. Esposito K, Giugliano D, Nappo F, Marfella R. the Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation*. 2004;110:214–219.
80. Ceriello A. Postprandial hyperglycemia and diabetes complications. *Diabetes*. 2005;54:1–7.
81. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295:1681–1687.
82. Service FJ, O'Brien PC. The relation of glycemia to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetologia*. 2001;44:1215–1220.
83. McCarter RJ, Hempe JM, Chalew SA. Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability. *Diabetes Care*. 2006;29:352–355.
84. Kilpatrick ES, Rigby A, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care*. 2006;29:1486–1490.
85. American Diabetes Association. Postprandial blood glucose. *Diabetes Care*. 2001;24:775–778.
86. American Diabetes Association. Standards of medical care in diabetes-2008. *Diabetes Care*. 2008;31(S1):S16–S24.
87. American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the management of diabetes mellitus. *Endocrine Practice*. 2007;13(S1):16.
88. El-Kebbi IM, Zeimer DC, Cook C, Miller CD, Gallina DL, Phillips LS. Comorbidity and glycemic control in patients with type 2 diabetes. *Arch Int Med*. 2001;161:1295–1300.
89. Gaede P, Veldel P, Larsen N, Jensen GVH, Parving H-H, Pederson O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–393.