

Effect of Intensive Treatment on Vascular and Other Complications of Diabetes Mellitus*

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Diabetes mellitus (DM) is a growing health problem in the United States afflicting over 18.2 million Americans. Before developing type 2 DM patients almost always have pre-diabetes. At least 20.1 million people in the United States ages ≥ 40 to ≤ 74 years have pre-diabetes. Research has shown that controlling blood glucose can delay or prevent type 2 DM from ever developing. Morbidity and mortality from DM most commonly result from the long-term complications of the disease. Data from several studies suggest that aggressive management of DM and its associated risk factors will lead to a reduction in these long-term complications. The term “intensive therapy” is being used for whatever strategy keeps blood sugar near normal, as well as for aggressive management of other associated risk factors such as lipid abnormalities and blood pressure. Intensive management of glycemia may have long-lasting benefits over conventional therapy. New clinical trials are being carried out to determine whether goals for intensive therapy should be lower than current goals while testing is being carried out on a variety of therapeutic strategies to determine the optimum methods to prevent diabetes complications. (*Clinical Cornerstone*, 2004;6[2]:40–50) Copyright © 2004 Excerpta Medica, Inc.

Morbidity and mortality from diabetes mellitus (DM) most commonly result from the long-term complications of the disease. The characteristic effects of type 2 DM are the principal causes of blindness and end-stage renal disease in the United States. In addition, cardiovascular (CV) disease (CVD) occurs at a young

age and is associated with more complications for patients with type 2 DM, and is their primary cause of death. However, data from several studies suggest that aggressive management of DM and its associated risk factors will lead to a reduction in these long-term complications.

KEY POINT

The microvascular effects of type 2 DM are the principal causes of blindness and end-stage renal disease in the United States.

WHAT IS “INTENSIVE THERAPY?”

The term *intensive therapy* began to be widely used after publication of the results of the Diabetes Control and Complications Trial (DCCT),¹ which was undertaken in patients with type 1 DM. The goal of the intensive therapy group was to maintain normoglycemia, but instead achieved glycosylated hemoglobin (A1C) of 7%, which was 2% lower than the conventional treatment group, resulting in a substantial reduction in complications of DM. The strategy

*This issue of *Clinical Cornerstone* contains references to off-label/unapproved uses of medications. Insulin is specifically indicated only for the treatment of hyperglycemia associated with diabetes mellitus. The above article discusses issues that are considered outside the scope of the FDA-approved indication for various drugs to treat diabetes.

used for intensive therapy in the DCCT consisted of 3 to 4 injections of insulin per day (usually using a basal-bolus approach) or a continuous infusion of insulin using a pump, as opposed to less frequent injections of mixed insulin.¹ The term *intensive therapy* was initially used to describe the approach of multiple-injection insulin therapy; however, in the United Kingdom Prospective Diabetes Study (UKPDS), the term also described oral agent therapy, if the aim was to keep the A1C as low as possible.² Now (and perhaps rightly so) the term is being used for whatever strategy keeps blood sugar near normal, as well as for aggressive management of other associated risk factors such as lipid abnormalities and blood pressure (BP), as reported in the Steno-2 study.³

Advantages of Intensive Therapy:

Data from Clinical Trials

The DCCT examined whether intensive treatment, with the goal of maintaining plasma glucose concentrations close to the normal range, could decrease the frequency and severity of microvascular complications in patients with type 1 DM.¹ In the primary-prevention cohort, intensive therapy reduced the risk for the development of retinopathy by 76% compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54%. Intensive therapy reduced the occurrence of microalbuminuria by 39%, albuminuria by 54%, and clinical neuropathy by 60%. Thus, intensive therapy effectively delayed the onset and slowed the progression of diabetic complications in patients with insulin-dependent DM.

KEY POINT

Intensive therapy effectively delayed the onset and slowed the progression of diabetic complications in patients with insulin-dependent DM.

To determine the long-term effects of intensive versus conventional treatment of type 1 DM in the DCCT, its cohort has been examined annually for 8 years as part of the follow-up study, Epidemiology of

Diabetes Interventions and Complications (EDIC).^{4,5} During the EDIC study, glycemic levels no longer differed significantly between the 2 original treatment groups, with an A1C of ~8% in both groups. Results were analyzed by intent-to-treat analyses, comparing the 2 original DCCT treatment groups. New cases of microalbuminuria occurred in the EDIC study in 6.8% of the participants originally assigned to the intensive treatment group, versus 15.8% of those assigned to the conventional treatment group, for a 59% reduction in odds, which was similar to the reduction at the end of the DCCT.⁵ Similarly, there was a significant reduction in odds for the development of clinical albuminuria and retinopathy.⁴

Thus, intensive management of glycemia may have long-lasting benefits over conventional therapy. This finding has far-reaching implications for how DM is, or should be, managed. The term *metabolic memory* has been used to propose the hypothesis that a period of near-normoglycemia will lead to long-term benefits, even if loss of glycemic control subsequently occurs.

Although the number of CV events remains low in this cohort, significantly fewer cases of hypertension have developed in the original intensive treatment group, and the carotid intima-media thickness (a surrogate for atherosclerosis) is also significantly low in this group.⁶ Therefore it is possible that a few years of good glycemic control, using insulin exclusively, may reduce the risk for CV events several years later.

In the UKPDS, patients randomized to “intensive therapy” had a significant reduction in microvascular complications no matter which therapy they received, despite the fact that because of the progressive nature of type 2 DM, diabetic control was suboptimal for many participants in the trial. Furthermore, the difference in A1C between intensive and conventional therapy groups was only 0.9%. In obese patients in the UKPDS, randomization to metformin resulted in a

KEY POINT

A few years of good glycemic control, using insulin exclusively, may reduce the risk for CV events several years later.

reduction not only in microvascular, but also in macrovascular, complications.⁷ However, when the UKPDS results were analyzed according to A1C achieved rather than on an intent-to-treat basis, macrovascular complications were also significantly reduced in patients who achieved good glycemic control.⁸

To determine the relationship between exposure to glycemia over time and the risk of macrovascular or microvascular complications in patients with type 2 DM, Stratton et al⁸ analyzed data from UKPDS patients independent of their randomization in the study. The incidence of clinical complications was significantly associated with glycemia. Each 1% reduction in A1C was associated with reductions in risk of 21% for any end point related to DM, 21% for deaths related to DM, 14% for myocardial infarction (MI), and 37% for microvascular complications. No threshold of risk was observed for any end point. Thus, any reduction in A1C is likely to reduce the risk of complications, with the lowest risk in those patients with A1C values in the normal range (<6.0%). Whether such a reduction can be achieved without risk of hypoglycemia is currently being tested in prospective clinical trials attempting normoglycemia.

Ohkubo et al⁹ used only insulin therapy in patients with type 2 DM. Patients randomized to intensive treatment received multiple insulin injections and had a significant reduction in the microvascular and macrovascular complications of DM, compared with the conventional treatment group. These results, as well as analysis of the DCCT treatment approach, suggest that multiple insulin injections, by reducing fluctuations in glucose for the same level of A1C, may lead to a greater reduction in complications than that by A1C reduction alone. Whether this difference is due to a reduction in postprandial excursions or just random fluctuation in glucose is not clear, because continuous measurements of glucose were not made in these studies.

Recently, studies have focused on the role of intensive therapy, especially as secondary prevention, to forestall CV events. Stress hyperglycemia with MI is associated with an increased risk of in-hospital mortality in patients with and without DM. The risk of congestive heart failure or cardiogenic shock is also increased in patients without DM.¹⁰ Insulin infusions have been shown to decrease mortality and adverse events in intensive care units.

Thus, in this setting of critical illness and MI, intensive therapy of DM may mean infusions of insulin intravenously during a hospital stay.

In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study, hospitalized patients presenting with an MI were randomized to an insulin infusion followed by 3 to 6 months of multiple insulin injections.¹¹ This treatment resulted in a 25% reduction in mortality following MI at the end of 1 year, and the benefit was maintained for another 4 years. The effect was most apparent in patients who had not previously received insulin treatment and who had a low CV risk. A recent study has reported that, on hospital admission with an MI, an infusion of insulin decreases markers of inflammation, oxidative stress, and abnormal fibrinolysis, and leads to a possible reduction in infarct size.¹²

Van den Berghe et al¹³ performed a prospective, randomized, controlled study on adults admitted to a surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy with an insulin infusion (maintenance of plasma glucose at a level between 80 and 110 mg/dL) or conventional treatment (infusion of insulin only if the plasma glucose level >215 mg/dL) and maintenance of glucose at a level between 180 and 200 mg/dL. Intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% ($P < 0.04$). Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%, and critical-illness polyneuropathy by 44%. Patients receiving intensive therapy were less likely to require

KEY POINT

Intensive insulin therapy to maintain plasma glucose to ≤ 110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.

prolonged mechanical ventilation and intensive care. Thus, intensive insulin therapy to maintain plasma glucose to ≤ 110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.

MULTIPLE RISK-FACTOR APPROACH TO INTENSIVE THERAPY

The Steno-2 study involved patients with type 2 DM at high risk for CV events because of microalbuminuria.³ The effect of a targeted, intensified, multifactorial intervention was compared with that of conventional treatment on modifiable risk factors for CVD in these patients over a mean follow-up period of 7.8 years. In an open, parallel-group design, 80 patients were randomly assigned to receive conventional treatment in accordance with national guidelines and 80 patients were to receive intensive treatment, with a stepwise implementation of behavior modification and pharmacological therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of CVD with aspirin.

The decline in A1C, systolic and diastolic BP, serum cholesterol and triglyceride levels, and urinary albumin excretion rate were all significantly greater in the intensive therapy group than in the conventional therapy group, although many patients did not meet predetermined goals. Patients receiving intensive therapy had a significantly lower risk of CVD (hazard ratio, 0.47), nephropathy (hazard ratio, 0.39), retinopathy (hazard ratio, 0.42), and autonomic neuropathy (hazard ratio, 0.37). Thus, target-driven, long-term intensive therapy aimed at multiple risk factors in patients with type 2 DM and microalbuminuria reduces the risk of CV and microvascular events by ~50%.³ To prevent macrovascular disease, a multiple risk-factor approach using various therapies may be necessary for CV event prevention.

THE BENEFITS OF INTENSIVE THERAPY

Hyperglycemia leads to a number of biochemical and structural abnormalities.¹⁴⁻¹⁶ In the short term, these include development of oxidative stress, endothelial dysfunction, and activation of coagulation. In the long term, glycosylation of proteins leads to formation of advanced glycosylation end products, which leads to stiffening of the arterial wall and other

connective tissue changes. Other biochemical abnormalities include accumulation of sorbitol in tissue, such as the nerve, kidney, and ocular lens, and activation of protein kinase C, an important mediator of tissue damage particularly in relation to microvascular disease. Another contributor to macrovascular pathogenesis is the increased level of free fatty acids present in states of insulin resistance, which may be reversed by intensive therapy. In addition, as the disease progresses and plasma glucose levels rise, hyperglycemia-induced reactive oxidative species may in turn contribute to activation of each of the above biochemical pathways.

APPROACHES TO INTENSIVE THERAPY TO PREVENT COMPLICATIONS

The lack of reversibility of established (clinically detectable) complications is well recognized. Early and aggressive correction of hyperglycemia may result in reversal of many of the biochemical abnormalities both in the short term as well as in the long term, but clinical features are rarely, if ever, reversed. Clinical trials are in progress with patients with very early abnormalities in plasma glucose (such as during the stage of “pre-diabetes”) to determine whether early intervention will lead not only to prevention of complications, but to prevention of DM itself.

To prevent the “imprinting” of target cells with the cellular and molecular changes described, achievement of near-normoglycemia must be attained early in DM. Near-normoglycemic remissions have occurred following the withdrawal of therapy in patients with type 2 DM who had received intensive treatment after presenting with severe hyperglycemia.¹⁷ Although it is difficult to determine the exact reason for these remissions, they might be due to amelioration of glucose toxicity by initial intensive glycemetic control.¹⁷

Intensive therapy can consist of multiple strategies, including diet to induce weight loss, exercise, frequent plasma glucose monitoring, and use of oral agents and insulin.

Intensive Lifestyle Change

Overweight and obesity are major contributors to both type 2 DM and CVD, and lifestyle change may be necessary for both the prevention and treatment of DM. The Diabetes Prevention Program randomly

assigned 3234 nondiabetic persons with elevated fasting and postload plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle modification program with the goals of a $\geq 7\%$ weight loss and ≥ 150 minutes of physical activity per week.¹⁸ Compared with placebo, the incidence of DM was reduced by 58% with the lifestyle intervention versus 31% with metformin; the lifestyle intervention was significantly more effective than metformin. Follow-up of this cohort may determine the value of this strategy in the prevention of CVD. Other clinical trials currently ongoing will determine whether early use of thiazolidinediones, blockade of the renin-angiotensin system, or even the early use of insulin can prevent the progression of type 2 DM and its macrovascular complications.

Although short-term weight loss has been shown to ameliorate obesity-related metabolic abnormalities and CVD risk factors, the long-term consequences of intentional weight loss in overweight or obese individuals with type 2 DM have not been adequately examined. The Look AHEAD (Action for Health in Diabetes) clinical trial is ongoing, with a primary objective of assessing the long-term effects (up to 11.5 years) of an intensive 4-year weight-loss program in overweight and obese individuals with type 2 DM.¹⁹ Approximately 5000 male and female participants, aged 45 to 74 years, who have type 2 DM and a body mass index of ≥ 25 kg/m² will be randomized to 1 of 2 groups. The intensive lifestyle intervention program is designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity, and will be compared with a control condition given DM support and education. The primary study outcome is timed to incidence of a major CVD event.

Hamdy et al²⁰ have demonstrated that 6 months of weight reduction and exercise improves macrovascular endothelial function and reduces selective markers of endothelial activation and coagulation in obese patients with insulin resistance syndrome, regardless of the degree of glucose tolerance. These results may have important implications for prevention of CVD in DM.

Intensive Pharmacological Therapy with Oral Agents

Intensive therapy with oral agents has been shown to lead to long-term benefits including possible

“remission” of DM in a few patients. However, oral therapy has so far not been shown to change the natural history of DM, resulting in a progressive loss of β -cell function and thereby “secondary failure” of these oral agents. Thus, it may not be possible to completely eliminate long-term complications by oral agents alone. In this context a study of intensive therapy after diagnosis is of interest. Banerji et al²¹ have defined and characterized the natural history of spontaneous near-normoglycemic remission with discontinuation of antidiabetic medication in 79 black non-insulin-dependent DM subjects. These patients had initially presented with very high plasma glucose concentrations. After intensive outpatient treatment, near-normoglycemic remission occurred within 8 to 10 months of insulin or sulfonylurea therapy, unrelated to the resolution of stress or significant weight loss.²¹

KEY POINT

Statin therapy for elevated cholesterol should be given to almost all people with type 2 DM.

Insulin

As indicated previously, the results from clinical trials of insulin for patients with type 2 DM are encouraging, partially because of the ability of insulin to lower glucose substantially more than oral agents.

Insulin has nearly unlimited potential to lower plasma glucose levels in patients with DM, and is capable of restoring near-normoglycemia—the primary treatment goal to prevent the onset and progression of long-term complications. Attainment and maintenance of near-normal glycemic control can be achieved with the use of insulin replacement strategies designed to simulate the physiologic nondiabetic patterns of insulin secretion in response to 24-hour postabsorptive and postprandial glucose profiles.

Addition of insulin to an oral agent may lead to large drops in plasma glucose, as reported in the Treat-to-Target Trial.²² Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% A1C in most overweight patients with

type 2 DM who have A1C between 7.5% and 10.0% when taking oral agents alone.²² In this study, insulin glargine caused significantly less nocturnal hypoglycemia than neutral protamine Hagedorn insulin, a result that should lessen physician resistance to initiating insulin. This simple regimen may facilitate earlier and effective insulin use in routine medical practice, thereby helping to achieve recommended standards of DM care.²²

As observed in the DCCT¹ and Ohkubo et al⁹ studies, a basal-bolus approach (long-acting insulin once daily, rapid-acting insulin with meals) may allow physiological insulin replacement that achieves not only better A1C reduction, but less fluctuation in plasma glucose with fewer complications.

KEY POINT

Addition of insulin to an oral agent may lead to large drops in plasma glucose, as reported in the Treat-to-Target Trial.

Lipid Management

Recent data suggest that patients with DM benefit greatly from aggressive lipids management, particularly statin therapy, irrespective of baseline cholesterol levels.

The Heart Protection Study provides direct evidence that cholesterol-lowering therapy is beneficial for persons with DM, even if they do not already have manifest coronary disease or high cholesterol concentrations.²³ Simvastatin 40 mg daily has been found to reduce the rate of first major vascular events by ~25% in a wide range of diabetic patients.²³ Statin therapy should now be a routine consideration for all diabetic patients at sufficiently high risk of major vascular events, regardless of their initial cholesterol concentrations. The target level for cholesterol, however, remains controversial. Low-density lipoprotein cholesterol (LDL-C) levels well below the target goal of <100 mg/dL may be desirable.

Blood Pressure

Data from several clinical trials have demonstrated that patients with DM may also require a lower

BP level to benefit from BP-lowering therapy. Based on these results, the American Diabetes Association has recommended a BP goal of 130/80 mm Hg to prevent the microvascular and macrovascular complications of DM.

The Heart Outcomes Prevention Evaluation (HOPE) study found that in patients with DM aged ≥ 55 years who had a previous CV event or ≥ 1 other CV risk factor, ramipril was beneficial in preventing CV events and overt nephropathy.²⁴ The CV benefit was greater than that attributable to the decrease in BP. This treatment represents a vasculoprotective and renoprotective effect for diabetic individuals.

CURRENT CLINICAL TRIALS IN PROGRESS

Several new clinical trials have recently been launched to determine the value of intensive therapy in type 2 DM. Among these the Action to Control Cardiovascular Risk in Diabetes (ACCORD) stands out by its size and the target goals for intensive therapy.²⁵ The 3 specific primary ACCORD hypotheses are as follows. In middle-aged or older people with type 2 DM who are at high risk for having a CV event because of existing clinical or subclinical CVD or CVD risk factors: (1) Does a therapeutic strategy that targets an A1C of <6.0% reduce the rate of CV events more than a strategy that targets an A1C of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%); (2) In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise high-density lipoprotein cholesterol/lower triglyceride levels and uses a statin for treatment of LDL-C reduce the rate of CV events compared to a strategy that only uses a statin for treatment of LDL-C; (3) In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of <120 mm Hg reduce the rate of CV events compared to a strategy that targets an SBP of <140 mm Hg? The primary outcome measure for the trial is the first occurrence of a major CV event, specifically nonfatal MI, nonfatal stroke, or CV death.

A new study, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D), is currently being carried out in patients with type 2 DM who have documented coronary artery disease (CAD).²⁶ The aim of this study is to compare treatment efficacy between initial elective revascular-

ization, either surgical or catheter based, combined with aggressive medical therapy and aggressive medical therapy alone. Also, this trial compares 5-year mortality in a strategy of hyperglycemia management with insulin sensitizers versus insulin secretagogues. It is designed to determine whether treatment targeted to attenuate insulin resistance can arrest or retard progression of CAD compared with treatment targeted to the same level of glycemic control with an insulin-providing approach.

Finally, Outcome Reduction with Initial Glargine Intervention²⁷ is a trial testing whether early (patients with impaired fasting glucose, impaired glucose tolerance, or newly diagnosed diabetes) intervention with insulin, as opposed to oral agents, will ameliorate the progression of β -cell dysfunction and CVD in type 2 DM.

SUMMARY

Intensive management of glycemia and other risk factors has been shown to decrease the risk of microvascular and macrovascular complications of diabetes. Ongoing clinical trials are assessing new goals and therapeutic strategies for intensive therapy to determine whether these complications can be reduced further.

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Dialogue Box

EDITORIAL BOARD

At one time it was thought that hyperinsulinemia might actually be the cause of some of the complications seen with DM. Did you mean to suggest in your article that the use of insulin might actually reduce the risk beyond its role in lowering glucose levels?

FONSECA

If I did, I overstated it since such a position lacks a solid scientific basis. Although there is evidence that insulin reduces inflammatory markers and oxidative stress, insulin sensitizers also reduce these same markers. The association between high insulin levels and CV risk does not appear to be a causative one; instead, high insulin levels indicate underlying insulin resistance which likely is the true culprit. The point I want to emphasize is the attainment of normoglycemia, whether accomplished with insulin or oral agents (such as insulin sensitizers) or a combination of the two. That is the real key to lowering the risk of complications.

EDITORIAL BOARD

Are you then saying that the lowering of inflammatory markers seen with insulin is an indirect benefit arising from improved glycemic control?

FONSECA

It may be but be aware that inflammatory markers can arise even before the development of hyperglycemia. Insulin reduces inflammatory markers as does insulin sensitizers, but we don't know whether the latter is a direct effect of the insulin sensitizer or whether these agents are just enhancing the effect of endogenous insulin.

EDITORIAL BOARD

Why would a patient with normal blood sugar develop inflammatory markers?

FONSECA

The real question is “what is a normal blood sugar?” Glucose levels can be thought of as a continuum—one in which we are changing our definition of “normal” all the time. Over the past decade, we have progressively lowered the glucose threshold for making the diagnosis of DM, lowering our definition of a normal fasting glucose. What we are currently calling “normal” may not actually represent absolute normalcy. We know that for every mg/dL rise in plasma glucose there seems to be an incremental risk for CVD. The relationship of glucose levels to the risk of complications is slightly different for microvascular disease and CVD. For the development of microvascular disease there appears to be a threshold in the 120s; since epidemiologic data suggested that ≥ 126 mg/dL increases the risk for microvascular disease, we define DM as a fasting plasma glucose at ≥ 126 mg/dL. In contrast, if the risk for CVD is a continuum in which there is no known “cutoff,” then there is no threshold for its development. Therefore, it would not be possible to determine a fasting glucose to define DM based on CV risk and that even in people who do not have a diagnosis of DM, the higher the glucose, the higher the risk. Somewhat arbitrarily, the glycemic threshold for metabolic syndrome was set at 110 mg/dL by the National Cholesterol Education Program and recently at 100 mg/dL by the American Diabetes Association.

EDITORIAL BOARD

The DCCT suggested that a period of “near-normoglycemia” provided long-term benefits with regard to the subsequent development of clinical albuminuria and retinopathy, even if loss of glycemic control subsequently occurred. What are the implications of this “metabolic memory” being achieved with an A1C as high as 7% and that no reduction in CV risk was demonstrated?

Dialogue Box

FONSECA

The original glycemic target in DCCT was actually an A1C <6%. The intent was to achieve normoglycemia, but the risk of hypoglycemia emerged as a limiting factor so they were forced to back off a bit to 7% and were still able to demonstrate a reduction in microvascular complications. As to why it failed to prove a reduction in CV risk, it's important to not overlook that the DCCT studied relatively young type 1 diabetics in whom macrovascular disease was not really an issue and thus the study likely lacked the statistical power to demonstrate a significant CV risk benefit. With regard to any notion that an A1C of 7% might represent some form of glycemic threshold, recognize that the rate of microvascular complications continued to drop with further declines in the A1C. However, the rate of decline was relatively low compared to the rising rate of hypoglycemia seen as the A1C fell further below 7%. On the basis of this, the investigators deemed a target A1C of 7% reasonable because that seemed to be the point where there was an appropriate trade-off between risk and benefit, in favor of benefit.

EDITORIAL BOARD

Does the “metabolic memory” phenomenon seen in DCCT occur in type 2 DM as well?

FONSECA

There are no data. There is simply no good study in type 2 DM where patients were controlled that well for 9 years. The ACCORD study, which will target an A1C of 6%, will likely shed light on this issue but the results won't be in until 2009.

EDITORIAL BOARD

In addition to achieving the targeted A1C, is it also important to control fluctuations in blood glucose as suggested by the study of Ohkubo and associates?

FONSECA

Possibly, since the benefit of this was also suggested in the DCCT. One can only assume that there was less variability of blood glucose in these studies because neither of the studies actually gauged glucose variability. Both the Ohkubo study and the DCCT subanalysis showed that for the same level of A1C, people treated with 4 insulin injections experienced fewer complications than those treated with 2 injections, and that presumably the former treatment group experienced fewer postprandial glucose excursions.

EDITORIAL BOARD

Has it been shown in any study that oral DM agents impact the natural history of DM as was demonstrated for insulin therapy in the DCCT?

FONSECA

No. In the UKPDS, neither insulin secretagogues nor metformin altered the progression of disease when used as monotherapy.

EDITORIAL BOARD

What about combination therapy?

FONSECA

The UKPDS did have a combination therapy group but it was very small. This group did not do particularly well in this study, although this may have been a subset of subjects who were going to do badly anyway. The ACCORD therapy should provide further data in this regard because it will undoubtedly require aggressive combination therapy since the goal in one of the treatment arms is to achieve an A1C <6%.

EDITORIAL BOARD

Is the glycosylated A1C a reliable indicator of glycemic control in a patient with a hemoglobinopathy such as sickle cell or thalassemia minor?

Dialogue Box

FONSECA

Generally not. Since that assay looks at the percentage of hemoglobin that is glycosylated A1C and since these disorders result in less overall hemoglobin A1 being present, the assay tends to underestimate hyperglycemia in such patients. In fact, whenever I see an A1C that is too good to be true, I become suspicious that I may be dealing with a hemoglobinopathy. So if you have a patient whose blood sugar is 250 mg/dL and he records at 200 mg/dL at home and his A1C is 6.2%, order a fructosamine. Fructosamine is a glycemic indicator like A1C but is obviously independent of hemoglobin. However, because of its shorter half-life, it reflects glycemic control over a shorter time period, ie, 4 weeks.

EDITORIAL BOARD

Do abnormal hemoglobins have the same rate of glycosylation as A1C?

FONSECA

Yes, they do. However, the lab measures only hemoglobin A. So if only 50% is hemoglobin A, and you have glycosylated 6% of it, the assay will indicate 3%.

EDITORIAL BOARD

Sickle cell–trait and β -thalassemia minor are fairly common hematologic disorders. Is it a fair statement to say that one should not rely on A1C in diabetic patients who have these disorders?

FONSECA

Not necessarily. It depends on how much of the hemoglobin is abnormal. For example, if the patient has sickle cell–trait and only a small amount of the hemoglobin is hemoglobin S, it's not going to have much of an impact. On the other hand, if the patient has a lot of hemoglobin S, then it will. The problem is that for the average person who is asymptomatic who comes into the diabetes clinic, you're unaware of the presence of the hemoglobinopathy, and the current methodology for A1C measurements used in most labs won't pick it up.

EDITORIAL BOARD

The HOPE study found that the angiotension-converting enzyme (ACE) inhibitor, ramipril, conferred benefit even in normotensive patients with diabetes who had other risk factors. Do you think that this represented a class effect provided by all ACE inhibitors or is this unique to ramipril?

FONSECA

There is a recent paper suggesting that all ACE inhibitors are not equal. Having said that, other studies, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, have failed to demonstrate any unique advantage of using ACE inhibitors in diabetic patients in terms of CV outcomes. Nevertheless, since all ACE inhibitors reduce proteinuria, I do prescribe them, usually the less expensive one, to my patients with diabetes. Based on what we know so far, I would use ramipril.