

Reevaluating Goals of Insulin Therapy: Perspectives from Large Clinical Trials

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KEYWORDS

- Diabetes • Insulin • Microvascular • Macrovascular
- Cardiovascular risk • Tactics • Goals • Glycemic control

The modern era of clinical research on treatments for diabetes dates back to the report of the University Group Diabetes Program (UGDP) published in 1970.¹ Although the UGDP yielded controversial and inconclusive results, it provided a stimulus for the design of several subsequent long-term clinical trials. The results of these trials have shown that improved glycemic control can reduce the microvascular complications of diabetes (eye, nerve, and kidney disease) and have led to treatment guidelines that are, at least in part, based on good evidence. However, a major question remains unanswered: what is the appropriate and safe target for glycemic control to minimize cardiovascular risks in patients with type 2 diabetes? This article surveys recent epidemiologic studies and interventional trials, examines current understanding of the natural history of type 2 diabetes, and proposes possible new goals and tactics for optimizing insulin therapy. The opinions expressed are our own and should not be taken as the views of any commercial entity or professional organization.

EPIDEMIOLOGIC ASSOCIATION OF HYPERGLYCEMIA WITH DIABETIC COMPLICATIONS

Hyperglycemia is the defining feature of diabetes and a key determinant of diabetic complications. Thus, the diagnosis of diabetes has been based on specific levels of hyperglycemia as advised by a group of experts assembled by the American Diabetes Association in 1997. This group examined the epidemiologic findings then available,

This work was supported in part by the Rose Hastings and Russell Standley Memorial Trusts. The authors have nothing to disclose.

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Endocrinol Metab Clin N Am 41 (2012) 41–56

doi:[10.1016/j.ecl.2012.03.003](https://doi.org/10.1016/j.ecl.2012.03.003)

endo.theclinics.com

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and proposed a rational basis for diagnosis and treatment.² **Fig. 1A** displays cross-sectional data that were cited in that report. In a population of persons not known to have diabetes, diabetic retinopathy found on fundoscopy was limited to the highest decile of the distribution of levels of fasting plasma glucose (FPG), glucose 2 hours after an oral glucose challenge (2-hour PG), and hemoglobin A1c (A1c). The upper boundary of the highest decile of values not associated with retinopathy was 109 mg/dL (6.1 mmol/L) for FPG, 154 mg/dL for 2-hour PG (8.6 mmol/L), and 5.9% for A1c. Thus, levels of hyperglycemia associated with retinopathy have provided the basis for defining diabetes. At present, the American Diabetes Association considers FPG greater than 126 mg/dL (7 mmol/L), 2-hour PG greater than 200 mg/dL (>11.1 mmol/L), and A1c greater than or equal to 6.5% to suggest the presence of diabetes, pending confirmation by a second test.³

More recently, other large epidemiologic studies have examined relationships between levels of hyperglycemia and cardiovascular disease.^{4–7} Examples of these are presented in **Fig. 1B** and **C**. **Fig. 1B** shows data prospectively collected from more than 4500 participants in the United Kingdom Prospective Diabetes Study (UKPDS) and analyzed epidemiologically. The risk of myocardial infarction was lowest at A1c less than 6.0%, and increased steadily at higher levels of A1c.⁶ **Fig. 1C** shows a meta-analysis including FPG samples from ~700,000 individuals with the lowest risk of coronary heart disease evident at values near 90 mg/dL (5 mmol/L) and increased risk at more than 100 mg/dL (5.6 mmol/L) either in the presence of known diabetes or

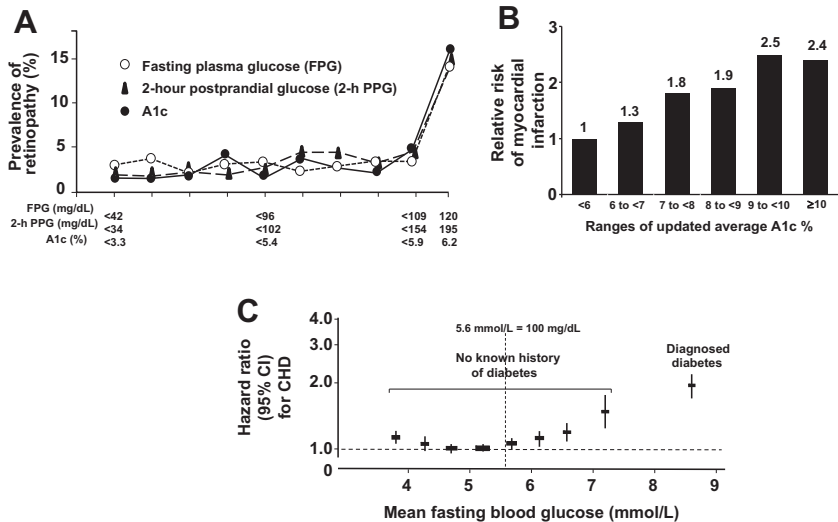


Fig. 1. Epidemiologic evidence for a relationship between hyperglycemia and the complications of diabetes. (A) The prevalence of retinopathy detected by fundoscopy in a cross-sectional population in the United States (NHANES III), displayed by deciles of fasting plasma glucose, glucose 2 hours after an oral glucose challenge, and A1c.² (B) Relative risk of myocardial infarction (adjusted for age, sex, and duration of diabetes) by ranges of updated average A1c over 10 years in the United Kingdom Prospective Diabetes Study (UKPDS) population, referenced to A1c less than 6.0%.⁶ (C) Hazard ratio for incident coronary heart disease (CHD) in a meta-analysis of 102 prospective studies (adjusted for age, sex, systolic blood pressure, and body mass index) by mean fasting blood glucose, referenced to 5.0 to 5.5 mmol/L (90–100 mg/dL).⁶

not.⁸ Such evidence continues to strengthen the case that increasing hyperglycemia is associated with increasing risk of both microvascular and cardiovascular disease starting from low levels of A1c or FPG.

EARLY IN DIABETES: INSULIN-AUGMENTING TREATMENT REDUCES MICROVASCULAR COMPLICATIONS

Despite epidemiologic evidence linking hyperglycemia with diabetic complications, skepticism that treating hyperglycemia might limit these complications persisted until the presentation of favorable results from the Diabetes Control and Complications Trial (DCCT)⁹ in 1993 and the UKPDS^{10,11} in 1997. Arguments against potential benefits of antihyperglycemic treatment included the view that diabetic complications could be mediated by means other than hyperglycemia^{12,13} and that adverse effects accompanying treatment, such as hypoglycemia, might lead to more harm than benefit.^{14,15} Findings of the DCCT and the UKPDS, which verified that the benefits of intensive treatment of hyperglycemia can outweigh the risks, are summarized in **Table 1**.

Despite studying different populations of patients (young adults with type 1 diabetes in the DCCT and middle-aged persons with type 2 in the UKPDS), these trials had several similarities. Both trials used insulin as an important part of the intervention. In the DCCT, multiple doses of insulin by injection or by pump delivery were used by all participants.⁹ In the UKPDS, the main randomized comparison was between a conventional regimen based on lifestyle therapy alone at the outset and more intensive treatment with basal (ultralente) insulin or a sulfonylurea.¹¹ An important substudy of the UKPDS mandated early addition of basal insulin to a sulfonylurea in one treatment group.¹⁶ Another similarity between the DCCT and the UKPDS was that intervention began early in the natural history of diabetes. Participants in the DCCT were known to have type 1 diabetes for an average of 6 years, presumably with only a short interval of hyperglycemia before diagnosis. Those in the UKPDS were treated within a year after diagnosis but, because of the known delay between onset of type 2 diabetes and diagnosis,¹⁷ were likely to have had an onset of diabetes for at least 4 years

	Number of Participants	Known Diabetes Duration (y)	Time of Randomized Treatment (y)	A1c (%) Difference Between Treatments	Reduction of Microvascular End Points	Reduction of Cardiovascular Events
DCCT ⁹	1441	6	6.5	~2.0 9.0 vs 7.1	Retinopathy 3-step progression 63% (<i>P</i> <.002) Albuminuria Micro 39% (<i>P</i> <.002) Macro 54% (<i>P</i> = .04)	CV composite 41% (NS)
UKPDS ^{10,11}	3867	<1	10	0.9 7.9 vs 7.0	Aggregate microvascular 25% (<i>P</i> <.001)	Myocardial infarction 16% (<i>P</i> = .052)

before randomization. Hence, the duration of hyperglycemia consistent with diabetes may have averaged about 6 years before entry to each trial.

The effect of intensive treatment on microvascular outcomes was also similar in the 2 trials. The difference of mean A1c levels between standard and intensive treatment in the DCCT ranged from 1.7% to 2.0% during the randomized comparison. In the UKPDS, both main treatment groups (lifestyle alone vs insulin or sulfonylurea) showed steady increases of A1c levels over time, but the median difference between the 2 groups over 10 years was 0.9%. The microvascular end points shown in **Table 1** were reduced by 39% to 63% in the DCCT, and the aggregate microvascular outcome in the UKPDS was reduced by 25% in the UKPDS. Despite the limitations of comparing trials with different designs, the findings in each suggest approximately 25% reduction of microvascular end points accompanying a 1% reduction of A1c. In contrast, effects on cardiovascular end points were not convincing. Neither a 41% reduction of a cardiovascular composite in the DCCT nor a 16% reduction of myocardial infarction in the UKPDS achieved statistical significance.

LATER IN TYPE 2 DIABETES: INTENSIVE TREATMENT OF HYPERGLYCEMIA YIELDS MIXED RESULTS

In addition to confirming the ability of glycemic intervention to reduce microvascular complications in both type 1 and type 2 diabetes, the DCCT and UKPDS results supported an A1c level of 7%, a level of control commonly achieved in each trial, as an appropriate goal for treatment. However, whether cardiovascular risk could be reduced by intensive glycemic control remained an open question. This finding prompted the design of 3 large clinical trials testing strategies targeting different levels of A1c in type 2 diabetes. The Veterans Affairs Diabetes Trial (VADT) began in 2000, and the Action in Diabetes and Vascular Disease: Preterax and Diamacron MR Controlled Evaluation (ADVANCE) and the Action to Control Cardiovascular Risk (ACCORD) trials both began in 2001. Initial reports from these trials first appeared in 2008 and 2009,^{18–20} and further reports followed.^{21–23}

The VADT, ACCORD, and ADVANCE trials were designed to avoid some limitations of the earlier ones. The limitations included the small numbers of participants and low cardiovascular risk in the DCCT and UKPDS populations, and the suboptimal levels of glycemic control achieved. By enrolling more participants with evidence of cardiovascular risk and targeting nearly normal glycemic control, the power to show potential cardiovascular benefits of intensive glycemic treatment was thought to be increased. In ADVANCE, the intensive treatment strategy was based on treatment with a sulfonylurea (gliclazide), and, in ACCORD and VADT, all available types of treatments were used, including extensive use of both basal and prandial insulins. Some of the main results are shown in **Table 2**.

All of these trials achieved a significant and sustained reduction of A1c levels in the intensive compared with the conventional treatment group. The average A1c level achieved with intensive therapy ranged from 6.4% in ACCORD to 6.9% in VADT; lower than in the DCCT and UKPDS. Intensive intervention in all 3 trials reduced at least 1 microvascular end point to a degree that, relative to the between-treatment differences of A1c levels, was comparable with the benefit shown in the DCCT and UKPDS. In contrast, none of the 3 trials showed an improvement of its main cardiovascular end point. In the case of ACCORD, an increase of total and cardiovascular mortality accompanying intensive therapy offset a 24% reduction of nonfatal myocardial infarction, leading to a small but nonsignificant reduction of the cardiovascular composite. A subsequent meta-analysis of data from these 3 trials and also from the UKPDS

Table 2

Microvascular end points and cardiovascular outcomes in Action in Diabetes and Vascular Disease: Preterax and Diamacron MR Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk (ACCORD), and the Veterans Affairs Diabetes Trial (VADT)

	Number of Participants	Known Diabetes Duration (y)	Time of Randomized Treatment (y)	A1c (%) Difference Between Treatments	Reduction of Microvascular End Points	Reduction of Cardiovascular Events
ADVANCE ¹⁹	11,140	8	5.0	0.7 7.3 vs 6.5	Retinopathy 5% ($P = .50$) Nephropathy composite 21% ($P = .006$)	CV composite 6% ($P = .32$)
ACCORD ¹⁸	10,251	10	3.7	1.1 7.5 vs 6.4	Retinopathy 33% ($P = .003$) Microalbuminuria 21% ($P = .0005$)	CV composite 10% (NS) Nonfatal MI 24% ($P = .004$)
VADT ²⁰	1791	11.5	5.6	1.5 8.4 vs 6.9	Retinopathy 2-step progression 23% ($P = .07$) Albuminuria Any increase 33% ($P = .01$)	CV composite 12% ($P = .14$)

showed no significant effect of intensive glycemic treatment on overall cardiovascular events or mortality,²⁴ but a significant 15% decrease of fatal or nonfatal myocardial infarction and ~2.5-fold increased risk of major hypoglycemic events. An exploratory subgroup analysis from this data-set showed greater potential for reduction of cardiovascular risk with intensive treatment in persons with diabetes without known prior cardiovascular events than in those with such a history (hazard ratio 0.84, confidence interval [CI] 0.74–0.94] vs hazard ratio 1.00, CI 0.89–1.13; for interaction, $P = .04$).²⁴

TEN YEARS AFTER CESSATION OF RANDOMIZED TREATMENT IN DCCT AND UKPDS: MICROVASCULAR BENEFITS PERSIST AND CARDIOVASCULAR BENEFITS ARE EVIDENT

The disappointing findings of the large intervention trials that enrolled high-risk participants later in the natural history of type 2 diabetes have provoked much discussion. To some extent, this ongoing debate has obscured further important reports from the DCCT and UKPDS populations. Key findings from these reports are shown in **Table 3**.

In 2005, the investigators of the DCCT and its Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study reported cardiovascular results from 10 years of observation after cessation of the randomized treatment comparison.²⁵ Participants in EDIC were not assigned to different regimens and maintained similar levels of glycemic control, with mean A1c levels that were slightly less than 8%. This observational study showed that the group previously using intensive insulin therapy had a statistically significant 42% reduction ($P = .02$) of risk of the broad cardiovascular composite end point used in the prior analysis. The commonly used composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was reduced by 56% ($P = .02$) in the prior intensive group. A later report from EDIC showed that large reductions (53%–59%) of retinopathy progression in the prior intensive group persisted after 10 years of follow-up.²⁶

Similarly, in 2008, the UKPDS investigators reported their 10-year follow-up findings.²⁷ The participants previously randomized to different therapies in the main UKPDS study had mean A1c levels that converged at approximately 8.0% during the period of follow-up. The risk ratio for various end points was lower in the prior insulin or sulfonylurea-treated group than in the conventionally treated group: 13% lower ($P = .007$) for all-cause mortality, 15% for myocardial infarction ($P = .01$), and

Table 3

Effect of treatments on microvascular end points and cardiovascular events at the end of randomized treatment and 10 years later in the DCCT and UKPDS

	Age at Entry (y)	Age After Randomized Treatment (y)	Age at 10 More Years of Follow-up (y)	Reduction of Microvascular End Points More than 17 y (%)	Reduction of Cardiovascular Events Over 17 y (%)
DCCT and EDIC ²⁵	27	34	44	Retinopathy 3-step progression 53–59 ($P < .0001$)	CV composite 42 ($P = .02$) CV death, MI, or CVA 57 ($P = .02$)
UKPDS ^{10,11} and UKPDS follow-up ²⁷	54	63	73	Aggregate microvascular 24 ($P < .001$)	Myocardial infarction 15 ($P = .01$) All-cause death 27 ($P = .002$)

24% for a microvascular composite ($P = .001$). In contrast with the end of randomized treatment, the mortality and myocardial infarction differences became statistically significant during the observational follow-up period because of the accrual of more events, whereas the relative differences between treatment groups were almost unchanged.

CONCEPTS DERIVED FROM EXPERIENCE WITH LARGE MEDICAL END POINT TRIALS TO DATE

The information obtained by long-term observation of participants in DCCT/EDIC and UKPDS sheds light on the findings from randomized treatment in ADVANCE, ACCORD, and VADT. Consider the following conclusions suggested by the 17-year to 20-year follow-up of the earlier trials together with short-term data from the more recent ones.

Early Treatment Reduces Complications

Glycemic intervention early in the natural history of diabetes, achieving A1c levels close to 7%, can (as hypothesized from epidemiologic data) reduce long-term risks of both microvascular and macrovascular events. However, the ~50% reduction of cardiovascular complications observed in DCCT/EDIC 10 years after cessation of 6.5 years of intensive therapy must be confirmed by further follow-up studies, especially because the mean age of participants at the time of this finding was only about 45 years. The UKPDS follow-up found quantitatively smaller reductions of cardiovascular events but also verified significant reduction of mortality.

Beneficial Effects of Treatment Persist for Years

Intensive glycemic treatment early in diabetes has a beneficial momentum that can persist for a decade or more, even when later treatment is less intensive. The DCCT/EDIC investigators suggested the term metabolic memory,^{25,28} whereas the UKPDS investigators proposed the term legacy effect for this phenomenon.²⁷

Harmful Effects of Preceding Poor Metabolic Control also Persist

A reverse legacy effect may also exist. Intensive glycemic intervention started late in the natural course of diabetes seems disappointingly ineffective in limiting cardiovascular events. That is, established cardiovascular disease that includes structural abnormalities (complex atheromatous plaques, diffusely sclerotic blood vessels) may no longer be reversible. Ineffective management of hyperglycemia, dyslipidemia, and hypertension may have caused or accelerated the development of these lesions, but improving metabolic control once these lesions are established may have little ability to reduce subsequent risk of clinically apparent cardiovascular events.

Intensive Intervention has Risks as well as Benefits

Vigorous treatment of hyperglycemia, like most forms of treatment, has risks and these may be more apparent in some individuals than others. Long duration of diabetes, which is often accompanied by significant injury to myocardial, neural, renal, and cognitive function, may expose patients to increased risk in addition to reduced benefit from treatment. The hazards include severe hypoglycemia and increased risk of unexplained cardiovascular death, as found in the ACCORD trial. Intensive glycemic treatment late in the course of type 2 diabetes, especially in individuals selected for high cardiovascular risk, may lead to some benefits but these may be offset by adverse effects. Thus, individualization of treatment aiming to improve the

benefit/risk ratio seems necessary in this setting, and new forms of treatment may facilitate this.

A1c LEVELS DURING THE NATURAL HISTORY OF TYPE 2 DIABETES: EVOLVING PATTERNS

The observations summarized earlier and the hypotheses derived from them have clinical implications. Among these are the potential for identifying high-risk subgroups and for developing safer and more effective therapies; these are beyond the scope of this article. Another application of these findings might be a new way of defining glycemic goals for insulin therapy.

Fig. 2 shows 3 possible patterns of glycemic control as reflected by A1c levels during the natural history of type 2 diabetes in a typical patient. The first pattern (see **Fig. 2A**) is adapted from an earlier review²⁹ and depicts experience that is consistent with clinical reports published up to around 2000,³⁰ an interval of time mostly preceding the application of epidemiologic findings and the results of the DCCT and UKPDS to specific goals for A1c. The figure illustrates vulnerability to developing gestational diabetes in young adulthood. In the hypothetical person shown, the diagnosis of diabetes was made at age 50 years but was preceded by a period of unrecognized hyperglycemia during which diabetic complications may have begun.¹⁷ This possibility is supported by data from patients recruited for the UKPDS at the time of diagnosis of type 2 diabetes at mean age 52 years.³¹ Of these newly diagnosed patients, 21% had retinopathy detected by fundoscopy, 18% an abnormal electrocardiogram, and 13% absent foot pulses. The mean level of A1c at diagnosis and entry into the run-in period that determined eligibility for randomization in the UKPDS was 11.6%.³¹ As in the UKPDS, initial treatment with lifestyle and an oral agent usually causes a good therapeutic response but, in many individuals, intensification of

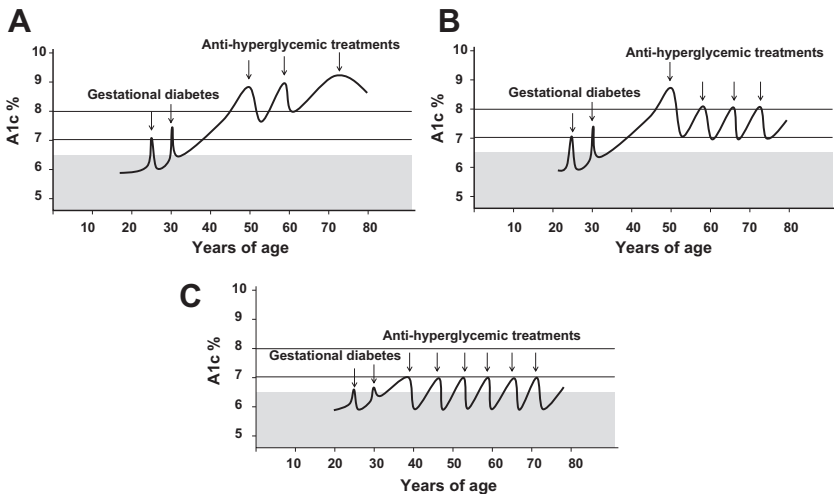


Fig. 2. Stylized patterns of A1c over the time course of type 2 diabetes, in relation to the time of diagnosis and therapeutic interventions. (A) A pattern typical of clinical experience before 1990. (B) A pattern typical of experience in the interval between 1990 and 2012. (C) A hypothetical pattern that might reflect future alteration of the natural history of type 2 diabetes, with timely diagnosis and early intensification of treatment.

treatment has been delayed until A1c levels had again risen to more than 8.0%. This delay has been termed clinical inertia.³² Hence, before 2000, the diagnosis of diabetes was frequently made years after the onset of overt diabetes, complications were often present at the time of diagnosis, improvements of A1c levels by treatment were seldom sustained, and patients often had A1c levels between 8% and 9% for much of the time after the onset of diabetes.

The second pattern (see **Fig. 2B**) depicts the A1c levels that have been sought during the last decade. The DCCT and UKPDS findings strongly influenced the recommendations of expert groups, with an A1c level of 7.0% being most often identified as the goal of treatment.³ Concurrently, cross-sectional studies of adults with known diabetes (including some treated with diet only) showed that mean levels of A1c decreased from nearly 8% in 2000 to 7.1% to 7.2% in 2006 and about half of these persons were maintaining A1c levels at 7.0% or less.^{33–35} This trend suggests that efforts to achieve an A1c level of 7% have frequently led to the intensification of therapy when the A1c level was around 8.0%. How much of the observed improvement of mean A1c levels has been caused by successful use of this therapeutic approach and how much to earlier diagnosis of diabetes is less clear. Information is limited about the period of time before diagnosis of diabetes or the frequency of complications that are already present at diagnosis.

The third pattern (see **Fig. 2C**) suggests A1c levels that might possibly be achieved if at-risk persons were routinely screened to diagnose diabetes soon after the onset of hyperglycemia. In this speculative scenario, therapy is started before A1c levels have risen to more than 7.0%, or soon after that, with the intention of preventing the earliest accrual of tissue injury. In this setting, an A1c level of 7.0% might be viewed not as a goal of treatment started at much higher levels, but as a threshold at which intensification of treatment should be considered. Hypothetically, for recently diagnosed patients, this strategy would produce a high ratio of benefit to risk and would be easy to implement.

INDIVIDUALIZATION OF INSULIN THERAPY FOR TYPE 2 DIABETES: NEW GOALS, NEW TACTICS

Both the reality of managing persons with well-established diabetes and the potential for earlier and more consistently effective treatment require further attention. The pattern of glycemic control over time shown in **Fig. 2A** should be relegated to history, but that in **Fig. 2B** continues to be appropriate for many patients. The demonstration of excess mortality accompanying more intensive glycemic management in a subgroup of participants in ACCORD calls for caution in further intensifying glycemic therapy using currently available methods of treatment once A1c levels between 7.0% and 8.0% have been established. Such individuals are presumably common among groups with long duration of diabetes,^{20,36} known prior cardiovascular events,^{24,36} and a history of prior A1c levels in excess of 8.5%.³⁷ Intensifying treatment of these persons when A1c levels are greater than 8.0%, using insulin when necessary, with the aim of maintaining glycemic control between 7.0% and 8.0% is consistent with the method used in the standard treatment group in ACCORD.^{22,38} Using this method, the ACCORD standard therapy participants achieved a median A1c level of 7.5%.²²

However, failing to seek near-normal glycemic control in the large number of lower-risk persons with type 2 diabetes is difficult to justify. Experience in the DCCT and the UKPDS suggests that patients with recently diagnosed diabetes and without other significant illnesses deserve treatment to prevent increases in A1c levels to more than 7.0%, with the aim of maintaining the pattern shown in **Fig. 2C**. The median level

of A1c in the insulin and sulfonylurea group of the UKPDS during randomized treatment was 7.0%, but the level in the first year after randomization was near 6.0% and the level 10 years later was nearer to 8.0%. However, this pattern of control resulted from initial allocation to monotherapy with agents that are now outdated (ultralente insulin, glyburide, and chlorpropamide), and progression to combination therapy regimens occurred only later in the study. With appropriate use of newer agents such as GLP-1 receptor agonists,^{39–42} DPP-4 inhibitors,^{39,43,44} or amylin receptor agonists^{45,46} in complementary combinations with other agents, including insulin, long-term maintenance of A1c levels between 6.0% and 7.0% without excessive risks may be achievable, especially when treatment is started when A1c levels have not yet risen to more than 7.0%. At the least, this is a testable hypothesis.

However, the difficulties are in the details of such proposals. How can high-risk individuals who have less potential for benefit and perhaps higher risk from targeting A1c levels lower than 7.0% be reliably identified, and how can these persons be matched to current and future forms of therapy that are best suited to them? What therapies are appropriate for lower-risk persons with newly diagnosed adult-onset diabetes, and, specifically, what may be the role of insulin? The first of these questions has been addressed in part already, but the second deserves further comment here. Insulin therapy is relevant in 3 common clinical scenarios early in type 2 diabetes.

Late-onset Type 1 Diabetes

There is an extensive literature on the significant population of persons who develop insulin-deficient diabetes in adulthood.⁴⁷ Type 1 diabetes with onset before age 20 years accounts for about 10% of all cases of diabetes in North America, but an approximately equal number of older persons develop a similar disorder, commonly termed latent autoimmune diabetes in adulthood (LADA).^{48–50} How the adult-onset version differs from typical type 1 diabetes is debatable, but its tendency to progress more rapidly to insulin dependency than type 2 diabetes is well documented. In the UKPDS, 12% of participants had glutamic acid decarboxylase (GAD) or other anti-islet antibodies at study entry, and the presence of these antibodies was a strong predictor of requirement for insulin therapy both immediately and over the course of 10 years of follow-up.⁵¹ Moreover, a subset of participants in the DCCT had residual β -cell function, and ~90% of these were older than 18 years at diagnosis.⁵² These patients with adult-onset type 1 with residual β -cell function retained endogenous insulin secretion longer when assigned to intensive, compared with standard, insulin therapy. Patients diagnosed with diabetes in adulthood can be identified as having LADA by measurement of islet cell or anti-GAD antibodies, and the need for testing may be suggested by clinical features common to this type of diabetes. These features include a family history of type 1 diabetes or other autoimmune syndromes, lack of family history of type 2 diabetes, lack of history of gestational diabetes, and rapid onset before age 40 years in nonobese persons. Such patients may not respond well to early treatment with regimens designed for type 2 diabetes, and, when insulin therapy is needed, it should not be delayed. Attention to sustained early increases of A1c levels to more than 7.0% despite conventional oral therapies would do much to address this need.

Symptomatic Hyperglycemia at Diagnosis

Patients are often diagnosed with type 2 diabetes because of symptoms associated with marked hyperglycemia. Textbooks often refer to excessive urination, thirst, and hunger as cardinal features, but probably just as common are fatigue, mental sluggishness, and skin infections. A1c levels greater than 10% accompanied by

symptoms at diagnosis suggest possible late-onset type 1 diabetes, but typical type 2 diabetes can present this way as well. In these patients, treatment with diet and oral therapies may be ineffective because of insulin resistance and reduced β -cell function caused by poor metabolic control (glucolipototoxicity).^{53,54} Short-term intensive insulin therapy has long been known to produce prompt symptomatic relief and to reduce many physiologic abnormalities, leading in some cases to a sustained remission of diabetes.^{55–57} Recent reports have verified this possibility in larger populations.^{58,59} Some evidence suggests that β -cell function may be better retained after early intensive insulin therapy for type 2 diabetes followed by oral therapy compared with oral therapy alone.⁵⁹

Diagnosis at the Time of a Cardiovascular Event

Because obesity and related metabolic disorders predispose both to diabetes and to cardiovascular disease, diabetes is frequently diagnosed at the time of a cardiovascular event.^{60,61} Intravenous insulin therapy is usually advised for treatment of hyperglycemia at such times. Physiologic and clinical studies provide a strong rationale for this, including evidence that the severity of myocardial injury and other complications may be reduced by timely administration of insulin.^{62–65} One early study suggested that intensive insulin treatment at the time of a myocardial infarction in persons with known diabetes reduces short-term mortality, and possibly also the risk of death from a subsequent infarction (case fatality). However, other studies have not confirmed these observations.^{66,67}

A large, ongoing clinical trial based partly on the foregoing rationale is studying the effects of basal insulin treatment early in type 2 diabetes in patients with high cardiovascular risk, most of whom have already had a cardiovascular event. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial has enrolled more than 12,500 participants with either type 2 diabetes treated with lifestyle with or without 1 oral agent.⁶⁸ Of the participants enrolled, 82% had previously known diabetes with a mean duration of 6 years, whereas the remaining 18% had either newly diagnosed diabetes, impaired glucose tolerance, or impaired fasting glucose levels. The mean A1c level in the whole population at study entry was 6.5%. High risk of cardiovascular events was required for study entry, and two-thirds of the population had a previous cardiovascular event. Participants were randomized to treatment with glargine targeting FPG levels of less than 95 mg/dL (5.3 mmol/L) or to standard step therapy with oral agents targeting A1c levels as considered customary at each site, generally less than 7.0%. The primary end point of the glycemic treatment comparison in ORIGIN is the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, but proteinuria, hypoglycemia, and progression of dysglycemic participants to overt diabetes will be studied as well. This trial ended in late 2011 after 7 years of randomized treatment, and the results have the potential to define both the risks and benefits of early use of basal insulin in the setting of high cardiovascular risk. A favorable balance of benefits versus risks in ORIGIN might support the early use of insulin in type 2 diabetes to prevent A1c levels from increasing to more than 7.0%, even for patients with established cardiovascular disease.

SUMMARY

The views of the last 2 decades are changing to a new approach to type 2 diabetes. The most compelling finding of long-term observations from the DCCT and UKPDS is that intensive glycemic control established early in the natural history of diabetes has a favorable benefit/risk ratio, but that 10 or more years are required to see the full

effects. The more recent clinical trials (ADVANCE, ACCORD, and VADT) showed that vigorous therapeutic efforts applied too late may yield limited short-term benefit, and may even cause more harm than benefit. That is, achieving near-normal glucose control in high-risk individuals may lead to increased cardiovascular mortality, the result that these trials were designed to prevent. Although the cause of increased cardiovascular risk accompanying intensive treatment remains uncertain, weight gain and hypoglycemia, both known consequences of insulin therapy, are obvious candidates. Thus, both glycemic treatment goals and the tactics used to achieve them require closer evaluation. For the present, while awaiting further evidence from analyses of completed studies and new findings from studies that are underway or in planning, we propose 3 courses of action.

First, for patients with 10 or more years' duration of suboptimally controlled type 2 diabetes and known microvascular or macrovascular complications, achieving A1c levels less than 7.0% may not be an appropriate goal. For such patients, similar to those who participated in ACCORD and the VADT, A1c levels between 7.0% and 8.0% may be appropriate as the target range in most cases, with 8.0% serving as the level at which to intensify treatment.

Second, for patients with newly recognized type 2 diabetes or A1c values known to be less than 8.0% most of the time since diagnosis, a usual target range between 6.0% and 7.0% may be appropriate, with intensification of treatment at any level more than 7.0%. How to treat patients with intermediate duration of diabetes and mild complications, or with long duration but with no apparent complications, is less clear and calls for further study.

Third, more information about the risks and benefits of all forms of therapy, including insulin, is urgently needed. Improved methods of epidemiologic analysis are now being brought to bear on this question, and several large studies longer than 3 years in duration are now underway testing various agents and their roles in the management of diabetes. Categories of patients for whom each of the main classes of agents (metformin, glucagonlike-peptide-1 agonists, insulins, and others) are preferred may soon be identified. Evidence is accumulating to suggest that use of insulin earlier in the natural history of adult-onset diabetes may be desirable, as in cases of LADA and diabetes presenting with acute illness or after a cardiovascular event. An increased level of detail, describing goals and tactics specific to different groups of patients, may soon be provided in clinical practice recommendations by professional advisory groups.

No one promised that the management of complex chronic diseases like diabetes would be straightforward. Hippocrates was right: "Life is short, and the Art long; the crisis fleeting, experiment perilous, and decision difficult."⁶⁹ However, efforts to better manage patients with diabetes continue to progress.

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