COMMENTARY

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Diabetes management: More than just cardiovascular risk?

Diabetes mellitus and its management have become the center of controversy in recent years. More emphasis is being placed on the potential for adverse cardiovascular outcomes with more aggressive glycemic control as well as on the potential for adverse cardiovascular events with newer antidiabetic therapies, and less on the importance of glycemic control, particularly early in the disease course.

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Although it is important to take new data into consideration when managing diabetes, it appears that the results of recent clinical trials are being misinterpreted and incorrectly applied to the wrong patient populations, and in the process, the results of older landmark clinical trials are being neglected. Inadequate glycemic control not only plays a role in cardiovascular risk, it also remains the leading cause of blindness, kidney failure, and nontraumatic lower-limb amputations in the United States.[1]

The results of ACCORD, VADT, and ADVANCE should not be extrapolated to younger, healthier patients

Although we need to recognize the potential for adverse cardiovascular outcomes with diabetes and its management, we cannot lose sight of the big picture—ie, that inadequate glycemic control confers both microvascular and macrovascular risk, and that the available data show that restoring near-euglycemia in patients with diabetes considerably reduces the risk of microvascular and macrovascular complications.

Several recently published clinical trials—the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[2] the Veterans Affairs Diabetes Trial (VADT),[3] and the Action in Diabetes and Vascular Disease (ADVANCE)[4]—failed to demonstrate improved cardiovascular outcomes with improved glycemic control. However, we should not take this to mean that glycemic control is unimportant.

In this article, we will discuss why the results of these recent clinical trials are not valid for the general population of patients with diabetes. We will review evidence from landmark clinical trials that clearly demonstrates that better glycemic control reduces both microvascular and macrovascular complications of diabetes (the "glucose hypothesis"). We contend that excellent glycemic control clearly decreases the microvascular complications of diabetes, and that results from long-term follow-up studies in both type 1 and type 2 diabetes show reduced rates of heart attack and stroke in patients treated intensively earlier in the course of their disease.[5,6]

EVIDENCE FOR THE GLUCOSE HYPOTHESIS

Diabetes Control and Complications Trial

The first major trial demonstrating that improved glycemic control provides benefit was the Diabetes Control and Complications Trial (DCCT).[7] This study enrolled 1,441 patients with insulin-dependent diabetes mellitus, 726 of whom had no retinopathy at baseline (the primary-prevention cohort) and 715 of whom had mild retinopathy (the secondary-intervention cohort).

Patients were randomly assigned to intensive therapy (three or more insulin injections per day or an insulin pump) or to conventional therapy with one or two daily insulin injections. They were followed for a mean of

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6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

During the study, the hemoglobin A_{1c} level averaged 9% in the control group and 7% in the intensively treated group. The cumulative incidence of retinopathy was defined as a change of three steps or more on fundus photography that was sustained over a 6-month period.

Effect on retinopathy. At study completion, the cumulative incidence of retinopathy in the intensive-therapy group was approximately 50% less than in the conventional-therapy group. Intensive therapy reduced the adjusted mean risk of retinopathy by 76% (95% confidence interval [CI] 62%–85%) in the primary-prevention cohort. In the secondary-prevention cohort, intensive therapy reduced the average risk of progression by 54% (95% CI 39%–66%). Intensive therapy reduced the adjusted risk of proliferative or severe nonproliferative retinopathy by 47% (P = .011) and that of treatment with photocoagulation by 56% (P = .002).

Effect on nephropathy. Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (P = .04) in the primary-prevention cohort and by 43% (P = .001) in the secondary-intervention cohort. The risk of macroalbuminuria was reduced by 56% (P = .01) in the secondary-intervention cohort.

Effect on neuropathy. In the patients in the primary-prevention cohort who did not have neuropathy at baseline, intensive therapy reduced the incidence of neuropathy at 5 years by 69% (to 3%, vs 10% in the conventional-therapy group; P = .006). Similarly, in the secondary-intervention cohort, intensive therapy reduced the incidence of clinical neuropathy at 5 years by 57% (to 7%, vs 16%; P < .001).

Effect on macrovascular events. In the initial trial, a nonsignificant 41% reduction in combined cardiovascular and peripheral vascular disease events was observed.

DCCT long-term follow-up

After DCCT concluded, the control and treatment groups' hemoglobin A_{1c} levels converged to approximately 8%. The two groups were then followed to determine the long-term effects of their prior separation of glycemic levels on micro- and macrovascular outcomes.[5] More than 90% of the original DCCT patients were followed for a mean of 17 years.

Intensive treatment reduced the risk of any cardiovascular disease event by 42% (95% CI 9%–63%; P = .02) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% (95% CI 12%–79%; P = .02). This result was observed despite separation of glucose control in the two groups only for the first 6.5 years. This beneficial effect of intensive early glycemic control has been termed *metabolic memory*.

Trials discussed in this article

ACCORD—Action to Control Cardiovascular Risk in Diabetes[2]

ADVANCE—Action in Diabetes and Vascular Disease[4]

DCCT—Diabetes Control and Complications Trial[7]

EDIC—Epidemiology of Diabetes Interventions and Complications[5]

UKPDS—United Kingdom Prospective Diabetes Study,[6,8]

VADT—Veterans Affairs Diabetes Trial[3]

United Kingdom Prospective Diabetes Study

A second major trial, the United Kingdom Prospective Diabetes Study (UKPDS),[8] assessed the effect of excellent diabetes control on diabetes complications in patients with type 2 diabetes. A total of 3,867 patients newly diagnosed with type 2 diabetes, median age 54, who after 3 months of diet treatment had mean fasting plasma glucose concentrations of 110 to 270 mg/dL, were randomly assigned to an intensive policy (with a sulfonylurea or insulin or, if overweight, metformin) or a conventional policy with diet. The aim in the intensive group was a fasting plasma glucose less than 108 mg/dL. In the conventional group, the aim was the best achievable fasting plasma glucose with diet alone; drugs were added only if there were hyperglycemic symptoms or a fasting plasma glucose greater than 270 mg/dL.

Over 10 years, the median hemoglobin A_{1c} level was 7.0% (interquartile range 6.2%–8.2%) in the intensive group compared with 7.9% (6.9%–8.8%) in the conventional group. Compared with the conventional group, the risk of any diabetes-related end point was 12% lower in the intensive group (95% CI 1%–21%, P = .029), the risk of any diabetes-related death was 10% lower (−11% to 27%, P = .34), and

'Metabolic memory' is the benefit from early intensive glycemic control many years later

the rate of all-cause mortality was 6% lower (−10% to 20%, $P = .44$). Most of the reduction in risk of any diabetes-related end point was from a 25% risk reduction (95% CI 7%–40%, $P = .0099$) in microvascular end points, including the need for retinal photocoagulation.

UKPDS long-term follow-up

In 2008, Holman et al published the results of long-term follow-up of patients included in the UKPDS.[6] In posttrial monitoring, 3,277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. Annual questionnaires were used to follow patients who were unable to attend the clinics, and all patients in years 6 to 10 were assessed through questionnaires.

Between-group differences in hemoglobin A_{1c} levels were lost after the first year. However, in the sulfonylurea-insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, $P = .04$) and microvascular disease (24%, $P = .001$), while risk reductions for myocardial infarction (15%, $P = .01$) and death from any cause (13%, $P = .007$) emerged over time as more events occurred. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, $P = .01$), myocardial infarction (33%, $P = .005$), and death from any cause (27%, $P = .002$).

Sulfonylureas are inexpensive but increase the risk of hypoglycemia

The long-term follow-up to the UKPDS, like the long-term follow-up to the DCCT, demonstrated metabolic memory: that is, despite an early loss of glycemic differences after completion of the trial, a continued reduction in microvascular risk and an emergent risk reduction for myocardial infarction and death from any cause were observed.

These long-term randomized prospective trials in patients with type 1 and type 2 diabetes clearly show that the glucose hypothesis is in fact correct: intensive glucose control lowers the risk of both microvascular and macrovascular complications of diabetes.

IS THERE DISCORDANCE BETWEEN OLDER AND MORE RECENT TRIALS?

If the results of these older landmark clinical trials are true, why did the more recent clinical trials fail to show cardiovascular benefit with stricter glycemic control, and in one trial[2] demonstrate the potential for harm? (ACCORD[2] found an increased death rate in patients who received intensive therapy, targeting a hemoglobin A_{1c} below 6.0%.)

The answer lies in the populations studied. ACCORD,[2] VADT,[3] and ADVANCE[4] were performed in older patients with prior cardiac events or with several risk factors for cardiovascular events. The study populations were picked to increase the number of cardiac events in a short time frame. Therefore, extrapolating the results of these studies to the younger population of patients with diabetes, most of whom have yet to develop macrovascular disease, is inappropriate.

The available evidence suggests that early aggressive management of diabetes reduces the risk of macrovascular disease, but that this benefit is delayed. In the UKPDS and DCCT trials, it took 10 to 17 years to show cardiac benefit in younger patients.

The results of ACCORD,[2] VADT,[3] and ADVANCE[4] are important when considered in the correct clinical context. Two of these trials did demonstrate some microvascular benefit as a result of better glycemic control in older patients, many of whom had long-standing diabetes. These studies suggest that, in patients who already have established cardiovascular disease or have several risk factors for cardiovascular events, a less-strict glycemic target may be warranted.

These trials should not be interpreted as saying that glycemic control is unimportant in older patients at higher risk. Rather, they suggest that an individualized approach to diabetes management, supported by the most recent American Diabetes Association guidelines,[9] is more appropriate.

Physicians may reasonably suggest a stricter A_{1c} goal (ie, < 6.5%) in certain patients if it can be achieved without significant hypoglycemia. Stricter glycemic targets would seem appropriate in patients recently diagnosed with diabetes, those who have a long life expectancy, and those who have not yet developed significant cardiovascular disease.[9]

However, in patients who already have developed advanced microvascular and macrovascular complications, who have long-standing diabetes, who have a history of severe

hypoglycemia (or hypoglycemia unawareness), or who have a limited life expectancy or numerous adverse comorbidities, a less strict glycemic target (hemoglobin A_{1c} < 8%) may be more appropriate.[9]

CARDIOVASCULAR RISK, HYPOGLYCEMIA, AND ATTAINING GLYCEMIC TARGETS

Metformin, in the absence of contraindications or intolerability, is generally the recommended first-line therapy to manage glycemia in patients with type 2 diabetes mellitus.[10,11] However, there are only limited data to direct clinicians as to which antidiabetic medication to use if further therapy is required to obtain glycemic control.

Much of the cardiovascular and mortality risk associated with aggressive diabetes management (ie, lower A_{1c} targets) is related to hypoglycemia. Thus, antidiabetic therapies that pose no risk or only a low risk of hypoglycemia should be chosen, particularly in older patients and in those with known cardiovascular disease. This may allow for better glycemic control without the risk of hypoglycemia and adverse cardiovascular outcomes.

However, in practice, clinicians continue to use a sulfonylurea as the second-line agent. Although sulfonylureas may appear to be a great option because of their low cost, they are associated with a higher risk of hypoglycemic episodes than other classes of diabetes drugs. We need to consider the frequency and cost of hypoglycemic episodes and the potential morbidity associated with them, because these episodes are a barrier to our efforts to achieve better glycemic control.

Budnitz et al[12] reported that from 2007 through 2009, in US adults age 65 and older, insulins were implicated in 13.9% of hospitalizations related to adverse drug events, and oral hypoglycemic agents (ie, insulin secretagogues) in 10.7%.

Quilliam et al[13] reported that hypoglycemia resulted in a mean cost of $17,564 for an inpatient admission, $1,387 for an emergency department visit, and $394 for an outpatient visit. Thus, the cost savings associated with prescribing a sulfonylurea vs one of the newer oral antidiabetic agents that do not increase the risk of hypoglycemia (unless used concurrently with insulin or an insulin secretagogue) can quickly be eroded by severe hypoglycemic episodes requiring medical care.

Moreover, once patients start to experience hypoglycemic episodes, they are very reluctant, as are their physicians, to intensify therapy, even if it is indicated by their elevated A_{1c}.

There are now seven classes of oral antidiabetic therapies other than insulin secretagogues (ie, other than sulfonylureas and the meglitinides nateglinide and repaglinide), as well as a few noninsulin injectable therapies (glucagon-like peptide-1 agonists), that are not associated with hypoglycemia. We believe these agents should be tried before prescribing an agent that carries the risk of hypoglycemia (ie, sulfonylureas).

If agents that do not cause hypoglycemia are used, more-aggressive glycemic targets may be achieved safely. The ACCORD study,[2] which included patients at high cardiovascular risk and aimed at an aggressive glycemic target of 6%, may have yielded much different results had agents that carry a high risk of hypoglycemia been excluded.

Of importance, cardiovascular risk is also influenced by the common comorbidities seen in patients with diabetes, such as hypertension and hypercholesterolemia. Intensive, multifactorial interventions that address not only glycemic control but also blood pressure and lipids and that include low-dose aspirin therapy have been shown to lower the risk of death from cardiovascular causes and the risk of cardiovascular events.[14] Likewise, smoking cessation is very important in reducing cardiovascular risk, especially in patients with diabetes.[15]

Also very important: blood pressure, lipids, smoking, aspirin

CLINICAL TRIALS IN CONTEXT

In conclusion, there is more to diabetes management than cardiovascular complications. Clearly, improved glycemic control decreases the risk of retinopathy, nephropathy, and neuropathy in patients with type 1 and type 2 diabetes. The DCCT and UKPDS extension studies further found that excellent glycemic control decreases rates of cardiac events.

The best way to treat diabetes may be different in otherwise healthy younger patients who have yet to develop significant complications than it is in older patients known to

have cardiovascular disease or several risk factors for cardiovascular events. The available evidence suggests it would be reasonable to aim for stricter glycemic targets in the younger patients and less stringent targets in the older patients, particularly in those with long-standing diabetes who have already developed significant micro- and macrovascular complications.

We should interpret clinical trials within their narrow clinical context, emphasizing the actual population of patients included in the study, so as to avoid the inappropriate extrapolation of the results to all.

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