

IN THE LITERATURE

More Is Not Always Better: Intensive Glycemic Control in Type 2 Diabetes

Commentary on The ACCORD Study Group: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358:2545-2559, 2008 and The ADVANCE Collaborative Group: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560-2572, 2008.

The effects of intensive glycemic control on cardiovascular disease (CVD) outcomes in “high risk” type 2 diabetes are the subject of much debate. The *New England Journal of Medicine* recently published results of 2 landmark clinical trials in patients with type 2 diabetes and CVD or multiple risk factors, ACCORD (Action to Control Cardiovascular Risk in Diabetes, N = 10,521) and ADVANCE (Action in Diabetes and Cardiovascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation, N = 11,140).^{1,2}

WHAT DO THESE IMPORTANT STUDIES SHOW?

The principal hypothesis driving ACCORD and ADVANCE was that intensive glycemic control to near-normal levels should reduce risk of major CVD events and death. Their results were resoundingly negative. Not only did intensive glycemic control fail to improve CVD outcomes in both trials, ACCORD was suspended 17 months early due to increased risk of death from all causes and CVD.^{1,2} Although risk of nonfatal myocardial infarction (MI) was reduced, there were greater numbers of fatalities from MI, congestive heart failure, and cardiac procedures in ACCORD participants treated intensively.¹ Therefore, the MI case-fatality rate appears to have actually increased.

In addition to evidence of harm in ACCORD, another safety concern in both trials was a high rate of severe hypoglycemic episodes (defined

by neurological compromise requiring assistance) in patients treated with intensive glycemic control.^{1,2} Frequency of severe hypoglycemia was increased 2- to 3-fold. For example, in ACCORD, the frequency was 16% in the intensive therapy group versus 5% in the standard therapy group ($P < 0.001$).

In order to put data from the ACCORD and ADVANCE trials in context, key aspects of their populations and interventions should be appreciated. Both studies enrolled older, type 2 diabetic patients (mean age > 60 years), about one-third of whom had a previous CVD event.^{1,2} Information about kidney disease was only provided in the ADVANCE article. Diabetic kidney disease as defined by macroalbuminuria was present in 3.4% (intensive glycemic control) and 3.9% (standard glycemic control), while microalbuminuria was present in 27% of each group.² Patients were excluded from ACCORD for a serum creatinine level greater than 1.5 mg/dL.¹ At baseline, kidney function (as measured by serum creatinine) appeared normal on average in both ACCORD and ADVANCE.

From a baseline mean hemoglobin A_{1c} (HbA_{1c}) level of 7.5%, the target was set at 6.5% for intensive control versus “local guidelines” for standard control in ADVANCE.² Mean HbA_{1c} levels of 6.5% and 7.3%, respectively, were achieved at study end with a time-weighted average difference of 0.67% between groups over a median of 5 years of follow up. The primary drug used to achieve intensive control was a sulfonylurea, gliclazide. Add-on metformin and insulin were frequently used in both groups, but use of thiazolidinediones was relatively uncommon (<20%). In ACCORD, the target HbA_{1c} for intensive control was less than 6%, compared with 7.0% to 7.9% for standard control.¹ HbA_{1c} fell rapidly in response to intensive therapy, reaching 6.7% by 4 months from a baseline of 8.1%; a stable median level

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of 6.4% was achieved by 1 year and sustained throughout the follow-up period (median time, 3.5 years). The standard-therapy group started at the same level, and HbA_{1c} dropped to 7.2% by 4 months and remained stable for the duration of the study. Drug therapies were chosen at investigator discretion. Half or more in both study groups used metformin, glimepiride, repaglinide, rosiglitazone, and/or insulin. Multiple drugs were usually required by the intensive glycemic control group, with most participants taking at least 3 agents.

The main difference between these studies was that death and fatal CVD outcomes were even more likely (ie, increased risk of harm) in the intensively treated group in ACCORD, whereas intensive therapy was essentially risk-neutral in ADVANCE.^{1,2} Based on generally similar study populations, the greater risk of adverse CVD outcomes may be related to the intensive glycemic control *strategy* in ACCORD. Possible reasons for risk enhancement may include: level of blood glucose achieved; magnitude or rate of change in glycemia; drug usage or interactions; severity and frequency of hypoglycemia; weight gain and fluid retention. Increased risk of death in ACCORD was not attributable to any specific drug, rosiglitazone in particular.^{1,3}

Despite the unexpected primary results and safety concerns in these trials, glimmers of hope may exist for intensifying glycemic control to near-normal levels in selected type 2 diabetic patients. First, in ACCORD, subgroups without prior CVD or with HbA_{1c} 8% or less demonstrated reduced risk for future CVD and death.¹ Second, in ADVANCE, risk of new-onset microalbuminuria and new or worsening nephropathy (primarily progression to macroalbuminuria) decreased.² However, albuminuria-related events are not clinical end points in the sense of defining morbidity or mortality.⁴ In the absence of apparent benefits on kidney function or failure, the value of “normalizing” glycemia is arguable in type 2 diabetic patients at high CVD risk. Additionally, the benefit-to-risk ratio of intensive glycemic control is more uncertain in the CKD setting because ACCORD excluded those with an elevated serum creatinine level.

HOW DO THESE STUDIES COMPARE WITH OTHER STUDIES?

Compelling evidence from clinical trials in types 1 and 2 diabetes have established that intensive glycemic control decreases risk of microvascular complications, especially kidney disease.⁵⁻⁹ However, earlier reports from the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) Study and UKPDS (United Kingdom Prospective Diabetes Study) did not inspire confidence that CVD was similarly affected.⁵⁻⁸ Yet, recent accounts of post-trial, long-term follow up indicate that risks of death and CVD events were in fact diminished by intensive glycemic control long after the interventions concluded (≤ 10 years of follow up), a so-called legacy effect.^{10,11} These risk reductions were achieved even though differences in HbA_{1c} between study groups disappeared by 1 year after the end of the interventions.

So, how can results from DCCT/EDIC and UKPDS be reconciled with those from ACCORD and ADVANCE?^{1,2,10,11} I suggest 3 principal reasons for differences between study outcomes: (1) Lower risk characteristics of study populations in DCCT/EDIC (young type 1 diabetic patients) and UKPDS (patients with new-onset type 2 diabetes). Both studies had exclusion criteria for CVD. DCCT/EDIC also excluded patients with hypertension or hypercholesterolemia. Similarly, lower-risk subgroups in ACCORD appeared to have reduced risk of MI, stroke, or CVD death with intensive glycemic control. (2) Less intensive glycemic control in DCCT/EDIC and UKPDS. For example, the mean HbA_{1c} at the end of the intensive intervention in UKPDS was 8.2% and remained between 7.5% and 8.5% over long-term follow up in both conventional and intensively treated groups. Thus, “intensive” therapy in UKPDS was akin to “standard” therapy in ACCORD and ADVANCE. There seems to be a point below which further benefits do not accrue and risks increase with intensive glycemic management. (3) Longer duration of follow up in DCCT/EDIC and UKPDS. Intensive glycemic control did not improve CVD outcomes or decrease risk of death until more than 10 years of follow up. The median durations of follow up in ADVANCE and ACCORD may

have been too short to assess long-lasting effects. Indeed, ADVANCE data suggest that CVD and death could be less frequent after 5 years of intensive glycemic control, but this observation must be considered hypothesis generating.²

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Clinical practice guidelines from professional organizations concerned with diabetes and CKD recommend a target HbA_{1c} less than 7%.^{4,12} The American Diabetes Association emphasizes the importance of individualizing therapy, which includes liberalizing this target in groups at greater risk of hypoglycemia.¹² The data from ADVANCE and ACCORD certainly do not provide evidence that the HbA_{1c} target should be lower.^{1,2} For that matter, neither do the long-term follow-up studies from DCCT/EDIC and UKPDS.^{10,11} Diabetic patients with CKD are at particularly high risk of death, CVD, and hypoglycemia.⁴ The ACCORD and ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension) trials raise a red flag about attempts to “normalize” glycemia in such a high-risk population. Even if long-term CVD and survival benefits should emerge, there may be a grave up-front price of overly intensive glycemic control.

Future studies should address fundamental questions about strategies for glycemic control (ie, level, magnitude and rate of change, specific drugs, and duration). Participants with CKD should clearly be included in these studies, considering that 30% to 50% of people with diabetes have, or will develop, kidney disease!⁴ Importantly, the standard reporting index for glycemic control will soon move away from HbA_{1c} to “estimated average glucose” (eAG).¹³ Unfortunately, the main validation study excluded patients with CKD or anemia, making applicability of eAG in these patients open to question. Therefore, validation of eAG in the diabetic CKD population should also be top priority.

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