Discord over ACCORD

What are we to make of the ACCORD study? This is a large, multicentre, randomized study to determine if aggressive treatment of cardiac risk factors will improve outcomes in a subset of higher-risk people with type 2 diabetes.

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The ACCORD study is a multicentre, randomized study to determine if aggressive treatment of cardiac risk factors will improve outcomes in a subset of higher-risk people with type 2 diabetes. On 6 February 2008, the National Heart, Lung and Blood Institute (NHLBI) of the National Institute of Health in the United States terminated one arm of the study 18 months ahead of schedule because of safety concerns. The group that received intensive efforts to lower blood sugars as measured by the glycosylated hemoglobin test, A1c, had increased mortality. There was considerable media coverage of the cessation of the trial and the finding that an attempt to achieve lower A1c targets was actually associated with more cardiovascular deaths.

According to the NHLBI press release, the study "enrolled 10 251 participants. Of these, 257 in the intensive treatment group have died, compared with 203 within the standard treatment group. This is a difference of 54 deaths, or 3 per 1000 participants each year, over an average of almost 4 years of treatment." The release went on to state that "the intensive treatment group had a target blood sugar goal, measured by hemoglobin A1c, of less than 6%. This is similar to blood sugar levels in adults without diabetes. The standard treatment group aimed for a target similar to what is achieved, on average, by those with diabetes in the United States (A1c of 7.0% to 7.9%) and lower than at study entry."[1] The intensive treatment group received multiple classes of glucose-lowering medication to reach this goal. These included combinations of metformin, glimepiride (a sulfonylurea agent), rosiglitazone, acarbose, insulin, and exenatide, a GLP-1 analog (a new class of anti-diabetic therapy not yet available in Canada).

There was substantial discussion in the press and scientific literature about the implications of this study for the treatment of type 2 diabetes. BC's Therapeutics Initiative (TI) published a newsletter on the subject.[2] Endocrinologists in BC took issue with TI's analysis of a press release and suggested that they were rushing to judgment in the absence of a peer-reviewed publication.[3] There was certainly a good deal of heated discussion among local academics about the continued relevance of the "glucose hypothesis" linking hyperglycemia with diabetes complications, including cardiovascular disease.

The ACCORD study has now published its results.[4] The article certainly confirms the earlier press release statement. The intensive-therapy glycemic group had a median A1c at 1 year of 6.4% with a relative increase in overall mortality of 22% and an absolute increase in mortality of 1.0% compared to the conventional group that had a median A1c of 7.5%. This is equivalent to one extra death in the intensive group for every 95 patients who were treated for 3.5 years. There is no "clear explanation for this higher mortality."[4]

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How are we to manage patients now? We all want to be careful to do no harm to high-risk people with Type 2 diabetes, so we need to look carefully at our treatment goals for this population because of their serious risks of cardiovascular disease and other complications.

Some points seem clear:

- All patients in ACCORD received focused care to improve hypertension and dyslipidemia, regardless of the glycemic targets. They did well. The death rates in all ACCORD

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patients were lower than the death rates for comparable groups of diabetics in other studies. Thus we should continue to make it a priority to control blood pressure and lipids to prevent cardiovascular events in people with type 2 diabetes.

- It is prudent to exercise caution in our blood glucose goals for patients at high risk for cardiac disease. The ACCORD study enrolled patients with diabetes in three categories (**Table**). Groups A and B have established atherosclerotic vascular disease (secondary prevention). I'm going to treat my patients in this population to the less-aggressive goal used in the most successful ACCORD subgroup and target an A1c of 7.0% to 7.9%. The Group C population is a "grey area." They have dyslipidemia, hypertension, smoking, or obesity as risk factors without proven cardiovascular disease. A very large percentage of people with type 2 diabetes probably meet this description. They have been lumped in with the proven atherosclerotic or higher-risk groups. The ACCORD article doesn't allow us to understand if the outcomes for this group differ. It is possible that subsequent publications may clarify this question. Until that time, the current ACCORD evidence mandates similar caution for these people to achieve an A1c target in the 7.0% to 7.9% range. For the rest of the lower-risk diabetic population that doesn't meet the ACCORD inclusion criteria, we have no evidence of harm in targeting a lower A1c if it can be accomplished without hypoglycemia.
- The ACCORD discussion does not help us determine glycemic goals for the prevention of other types of diabetic complications relating to the microvasculature such as retinopathy, neuropathy, and nephropathy. The existing literature suggests a strong causative relationship between elevated blood sugar and microvascular complications. Therefore once we have stratified the A1c goal range for a patient according to cardiovascular risk, we should probably try to bring the A1c into the lower portion of that target range to minimize eye, nerve, and kidney disease risks.

Table. ACCORD inclusion criteria for cardiovascular disease.[5]

A. Presence of clinical cardiovascular disease.
- Previous myocardial infarction (MI).
- Previous stroke.
- History of coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy).
- History of carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aorta aneurysm, femoral or popliteal bypass).
- Angina with ischemic changes (resting ECG), ECG changes on a graded exercise test (GXT), or positive cardiac imaging study.

or

B. If no clinical cardiovascular disease, evidence in the last 2 years suggesting a high likelihood of cardiovascular disease. Specifically, the presence of one of the following:
- Microalbuminuria.
- Ankle brachial index < 0.9 (by simple palpation).
- LVH by ECG or ECHO.
- > 50% stenosis of a coronary, carotid, or lower extremity artery.

or

C. The presence of at least two of the following factors that increase CVD risk:
- On lipid-lowering medication or untreated LDL-C >130 mg/dl (3.38 mmol/l).
- Low HDL-C (< 40 mg/dl (1.04 mmol/l) for men and < 50 mg/dl (1.29 mmol/l) for women).
- On BP lowering medication or untreated SBP >140 mm Hg or DBP > 95 mm Hg.
- Current cigarette smoking.
- Body mass index > 32 kg/m^2.

This is a reasonable approach based on a scientific analysis of the large well-designed prospective ACCORD trial. A second important study, the ADVANCE trial, was published in the same journal.[6] This study did not show increased mortality with a glycemic goal of A1c below 6.5%. However, the types of pharmacologic interventions that were used differ from ACCORD and the patient population was at lower cardiovascular risk. Importantly, the trial reminded us of the main demonstrated benefit of lower glycemic control through a 21% relative reduction in nephropathy.

Overall, then, we need to reconsider our approach for patients with type 2 diabetes with known cardiovascular disease or risks such as hypertension, dyslipidemia, and smoking. Treat their blood pressure and cholesterol. Target an A1c result as low as can be accomplished within the 7.0% to 7.9% range.

With this approach it should be possible to balance cardiovascular safety and meaningful reductions in microvascular complication risks.

Competing interests

Dr Dahl has received speaking fees or research grants from most of the major pharmaceutical companies.

References

1. National Institutes of Health. For safety, NHLBI changes intensive blood sugar treatment strategy in clinical trial of diabetes and cardiovascular disease. NIH News. 6 February 2008. www.nih.gov/news/health/feb2008/nhlbi-06.htm (accessed 26 June 2008).
2. Therapeutics Initiative. Glycemic targets in type 2 diabetes. Therapeutics Letter 68, January–February 2008. www.ti.ubc.ca/en/letter68 (accessed 26 June 2008).

3. Ur E, Dawson K. Glucose targets [letter]. BC Med J 2008;50:243.
4. Action to Control Cardiovascular risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545-2559.
5. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial Protocol. 11 May 2005. www.accordtrial.org/web/public/documents/Protocol%20All%20Chapters.pdf?CFID=189977&CFTOKEN=78468784.
6. ADVANCE Collaborative Group. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358; 2560-2572.

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