ACCORD and ADVANCE: a tale of two studies on the merits of glycaemic control in type 2 diabetic patients

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Keywords: glycaemic control; type 2 diabetes

Insight from the present: ACCORD and ADVANCE

Amid much media interest, preliminary data of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study were released in view of the unexpected finding that type 2 diabetic (T2DM) patients in the intensive blood glucose-lowering treatment arm [target glycated haemoglobin (HbA1c) <6%] had an increased risk of cardiovascular death compared to those in the conventional treatment arm (target HbA1c 7–7.9%) (http://www.nhlbi.nih.gov/health/prof/heart/other/accord/index.htm).

The ACCORD study, sponsored by the National Institute of Health, was a large clinical trial of 10 251 T2DM patients designed to determine the best clinical approach to reduce the high rate of cardiovascular morbidity and mortality seen in T2DM patients at a high vascular risk. The main question asked being if an intensive glycaemic target as compared to the conventional one would result in favourable cardiovascular outcomes [1].

In the intensive arm, 257 patients died, compared with 203 within the conventional (standard) treatment arm. This was a difference of 54 deaths, or 3 per 1000 participants each year, over an average treatment duration of ∼4 years. Importantly, it should be noted that these death rates in both arms were lower than those seen in similar populations in other studies. Interestingly, the press release also appeared to suggest that in the intensive arm non-fatal cardiovascular disease (CVD) events were less frequent; however, if an event did occur it was also more likely to be fatal.

In view of these unexpected results, the blood glucose-lowering sub-study of ACCORD was terminated 18 months prior to completion and all patients were switched to the pressure-lowering conventional treatment arm. However the lipid and blood pressure-lowering sub-studies are continuing, albeit now in the setting of conventional treatment targets for glycaemic control.

Patients who were eligible for the study were T2DM patients aged between 40 and 79 years with previous history of CVD, or those between 60 and 79 years with no history of CVD events; additionally those at high risk of CVD events (e.g. the presence of microalbuminuria, left ventricular hypertrophy) were also included. An HbA1c > 7.5% on stable diabetes therapy and preserved renal function...
with a serum creatinine <1.5 mg/dl (132.6 μmol/l) were used as inclusion criteria. Patients with current symptomatic heart failure and a history of NYHA III and IV were excluded.

The early termination of the ACCORD trial was given prominence and highlighted in the medical and lay press, and resulted in heated discussions on whether new glycaemic targets and guidelines should be introduced in T2DM patients, and if existing targets should be revised for patients with similar characteristics to those studied in the ACCORD trial.

Possibly as a ‘response’ to the anxieties raised by ACCORD, another study, ADVANCE (Action in Diabetes and Vascular Disease) [2], released an interim report suggesting that, at least in this study, there was no evidence that intensive treatment to lower blood-glucose levels in T2DM patients increased their risk of cardiovascular mortality (http://www.advance-trial.com/static/html/healthcare/home.asp).

ADVANCE studied 11 140 T2DM patients at high risk of CVD who were randomized to intensive or standard glucose-lowering treatments and its interim analysis was based on more than twice as many data and similar levels of glucose control as in ACCORD.

However, despite these reassuring data, it is still unclear whether the mortality results from ADVANCE show a benefit for intensive glucose lowering or a neutral effect. Importantly, there was no indication of harm noted in the ADVANCE trial. ADVANCE aimed for HbA1c levels of 6.5% or below, with an achieved HbA1c level of 6.4%, comparable to the ‘achieved HbA1c levels’ in the intensive arm in ACCORD; the standard treatment arm in ADVANCE achieved an HbA1c level of 7%, slightly below the 7.5% level reached in ACCORD.

These discordant results unfortunately lead to many more questions than answers, many of which cannot be resolved until more data are available from the respective studies. Can, at present, apparently contradictory results from ACCORD and ADVANCE be fairly compared? And importantly, where do these results leave the physician treating patients with T2DM?

Certainly differences do exist between these two trials that require highlighting: ACCORD allowed any treatment whatsoever to reach target glucose levels, whereas in ADVANCE, all patients in the intensive group started treatment with modified-release gliclazide. However, as many patients in ADVANCE could not reach the goal, multiple therapies were used similar to ACCORD.

Approximately one-third of the patients in both studies had a prior history of CVD; however, the average age in ADVANCE was slightly higher (66 in ADVANCE, 62 years in ACCORD), and patients had a shorter duration of diabetes in ADVANCE (8 years in ADVANCE, 10 years in ACCORD).

Further HbA1c levels were slightly lower at baseline in ADVANCE patients, but their blood pressure was higher than those in ACCORD. Finally, ADVANCE was aiming only for an HbA1c of 6.5%, while ACCORD was aiming for values <6.0% although the target achieved seemed to be slightly higher (6.4%).

Lessons from recent times: UKPDS and STENO-2

Two other major trials, the UKPDS and the STENO-2, help us to understand the role of metabolic control on vascular complications in T2DM patients. In the UKPDS study, the combined risk of diabetic chronic micro- and macrovascular complications was lower in individuals with better glycaemic control, with any reduction in HbA1c associated with a reduced risk, the lowest being patients with HbA1c in the normal range (<6.0%) [3].

Importantly, a multifactorial intervention in T2DM patients similar to the one implemented in the STENO-2 study should be the goal we should follow in all our patients. In the STENO-2, the mean follow-up of 7.8 years, the decline in HbA1c, systolic and diastolic blood pressure, lipids and urinary albumin excretion rate were all greater in the intensive-therapy group than in the conventional therapy group [4]. T2DM patients receiving intensive therapy also had a significantly lower risk of ~50% in micro- and macrovascular diabetic complications. However, of interest, in this study a relatively small proportion of patients (~20%) in the intensive arm achieved the HbA1c targets (HbA1c < 6.5%), as compared to ~60–70% for blood pressure and lipid targets; nevertheless, benefits in terms of CVD outcomes remained significant in the short (7.8 years) and the subsequent long-term follow-up assessment at 13 years, even when mean HbA1c levels assessed at the later time point had merged and were similar at ~8% for both treatment arms [4,5].

Two other questions that arose following the release of ACCORD were why, in the intensive glycaemic control arm, less CVD events (myocardial infarctions mainly) were observed, and why, when they did occur, were there more severe and more unexpected sudden deaths in the absence of a myocardial infarction?

Therefore, is a ‘lower’ HbA1c of benefit in the prevention of CVD events and why would ‘tight glycaemic control (HbA1c < 6.5%)’ be potentially detrimental if an event was to occur?

Although there are several differences in the study populations, it may be of value to go back and review CVD data from the UKPDS study. When UKPDS investigators analysed >500 myocardial infarcts that occurred during the study, of which 52% were fatal, multi-variate analyses (albeit post hoc) documented that patients with fatal myocardial infarct had a higher HbA1c around the time of diagnosis, many years before the event, compared with those with non-fatal myocardial infarcts [6].

Another post hoc analysis of the same study showed an increased risk of ischaemic heart disease of 11% for each increment of 1% in HbA1c, with the increased risk starting, interestingly, at an HbA1c > 6.2%, the upper range of normal values [7]. However, it is important to note that UKPDS failed to find a significant reduction in cardiovascular events even with excellent glucose control, but with a borderline significance ($P = 0.052$) for myocardial infarction in favour of the intensive glycaemic control [8].

It is possible to conceive that, once an event occurs, if the current glycaemic control is too tight, this may predict an unfavourable outcome in view of the known detrimental cardiac effects of hypoglycaemic episodes and events [9,10].
The adverse cardiac effects of hypoglycaemia, partly a consequence of the resultant over-activation of the sympathetic nervous system and cardiac dysrhythmias, are seen in those at most risk of ischaemic heart disease, and importantly, in patients with diabetes who are known to be at high risk of sudden cardiac death and ventricular arrhythmias [11,12].

These observations might in part suggest a potential explanation on the high incidence of sudden cardiac death observed in the intensive glycaemic control arm of the ACCORD population; importantly, we should emphasize that these comments remain pure speculations, and that more data and analyses from these studies are needed before one can conclusively comment on the preliminary ACCORD and ADVANCE results.

We should also emphasize that the American Diabetes Associations (ADA) continues to advise most people with diabetes to strive for an HbA1c of <7% but it also stresses the need for individualization of treatment goals depending on patient factors including comorbidities [13]. In view of the recent controversy, the ADA has advised that T2DM patients who have existing CVD or multiple cardiovascular risk factors should consult with their healthcare team about their ‘individualized’ treatment goals.

Conclusion

In T2DM patients with known ischaemic heart disease, an HbA1c between 6.5 and 7% is a reasonable target at present, as no clear cardiovascular benefits have been demonstrated if HbA1c is any lower. In view of the ACCORD data, albeit preliminary and not fully reported or analysed, such a relatively conservative treatment goal for HbA1c is reasonable at this stage.

In T2DM patients with chronic kidney disease, known to be at high risk of CVD, a similar treatment target, which is often difficult to attain, is reasonable at present and more so for such patients on renal replacement therapy who are at a greatly increased risk of ischaemic heart disease events.

Multifactorial interventions similar to STENO-2 should be the goal of therapy as there is clear evidence for the long-term sustained benefits on CVD outcomes of such an approach where benefits in terms of CVD outcomes remained significant up to a period of 13 years [5].

Conflict of interest statement. None declared.

References