Intensive glucose control and cardiovascular disease in type 2 diabetes – should we change the recommended target for glycated hemoglobin?

Commentary to ACCORD and ADVANCE trials

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Not only was ultra-tight glucose control aiming for a goal of glycated hemoglobin (HbA_{1c}) level below 6.0% linked to excess deaths in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, but it was no more effective than standard therapy aiming at a HbA_{1c} between 7.0% and 7.9% in reducing cardiovascular events among patients with type 2 diabetes.[1]

Also, the ADVANCE (Action in Diabetes and Vascular Disease) trial failed to demonstrate beneficial effects on cardiovascular disease of intensive glucose control aiming at a HbA_{1c} level below 6.5% compared to standard therapy with a target HbA_{1c} <7.0%.[2] No difference in mortality between the 2 treatment groups was seen in this trial.

Since HbA_{1c} remains one of the most important risk factors for cardiovascular disease including all cause mortality in type 2 diabetes in observational studies[3] the results from ACCORD and ADVANCE are both surprising and disappointing. With a potential hazard of an increased risk for death with intensive glucose control, the obvious but intriguing question whether we should loosen current guidelines for the target value of HbA_{1c} arises.

In my mind there are several reasons why this should not be the case based on the current evidence. So let us review the case files in further detail.

The ACCORD study enrolled 10,251 middle-aged or older type 2 diabetic patients with either evidence of or increased risk for cardiovascular disease. The median HbA_{1c} at randomization was 8.1%. Patients in the intensive treatment group was in contact with the diabetes team

every month throughout the follow-up period with the aim of rapidly reducing HbA_{1c} levels below 6.0% while the standard group was seen every 4th month. A very fast and stable reduction in HbA_{1c} was seen within the first 6 months of the study with median levels of 6.4% and 7.5% in the intensive and standard therapy group, respectively. The primary endpoint was a composite of cardiovascular events with total mortality being a secondary endpoint. Planned follow-up was five years but the study was stopped by the data monitoring committee due to an excess number of mortalities with intensive therapy after a mean follow-up time of 3.5 years. 257 patients in the intensive compared to 203 patients in the standard group died (hazard ratio [HR] 1.22, 95% CI 1.01–1.46, p = 0.04). The excess deaths with intensive treatment were mainly from cardiovascular causes, with 41 more patients dying from strokes, heart attacks, congestive heart failure, arrhythmia, or invasive interventions than in the standard therapy group (135 vs. 94 deaths, HR 1.35, 95% CI 1.00–1.76, p = 0.05). The cardiovascular deaths appeared to be spread evenly among the different specific causes. At this time no difference was seen between groups for the primary endpoint, although the total number of events was lower with intensive therapy (HR 0.90, 95% CI 0.78–1.04, p = 0.16).

The ADVANCE study enrolled 11,140 patients with type 2 diabetes with a history of major macro- or microvascular disease or at least one other risk factor for cardiovascular disease. The intensive therapy group aimed at a HbA_{1c} value of ≤6.5%, with no specific target value given in the

standard therapy group but emphasizing that current guidelines recommend a target glycated hemoglobin of ≤7.0% for most patients with type 2 diabetes. Also in this study, the primary endpoint was a composite endpoint but in this case a mixture of both macro- and microvascular events. After a median follow-up time of 5 years, the mean HbA_{1c} level was 6.5% with intensive therapy compared to 7.3%. Although a significant risk reduction with intensive glucose lowering therapy was seen for the composite endpoint, no significant effects were seen on cardiovascular disease (HR 0.94, 95% CI 0.84–1.06, p = 0.32). No difference between groups was seen for mortality with 498 deaths in the intensive group compared to 533 deaths with standard therapy. Just as in the ACCORD study the use of glucose lowering drugs and combinations of these was more frequent in the intensive therapy compared to the standard group with the largest differences being for gliclazide (cornerstone of intensive treatment in the study) and insulin.

In short, in the ACCORD trial HbA_{1c} levels were 6.4% and 7.5% in the intensive and standard therapy group, respectively, while levels were 6.5% and 7.3% in each of the two treatment groups in the ADVANCE trial. So, how can mortality data yield so different results with glucose control being almost identical in these studies?

First, the frequency of hypoglycemia was much higher in the ACCORD (3.3%/year) than in the ADVANCE study (0.7%/year). The effect of hypoglycemia appears to be of great importance. In the ACCORD study, although the investigators stated that this was not a mediator of the increased mortality associated with intensive treatment in a direct linkage analysis, they did find that hypoglycemia was associated with increased mortality in both treatment groups.

Second, it is essential to look at the drugs used to achieve the very tight glucose control in the intensive treatment groups. No formal titration guidelines from the ACCORD study have been published. The choice of medication in a given participant was based on clinical judgment and characteristics of participants. The use of combination therapy of different classes of glucose lowering drugs was widespread in the intensive group. Also, the use of insulin as well as newer drugs such as thiazolidinediones and incretins was significantly higher in the intensive group than in the standard group. Especially the widespread use of thiazolidinediones is controversial.[4]

Third, severe weight gain of more than 10 kg was seen in almost 30% of patients in the intensive group in the ACCORD study. It cannot be ruled out that this is a piece of the increased mortality puzzle.

Fourth, it is important to look at the methods used to obtain the treatment goals in the two trials. In the ADVANCE trial a predefined titration protocol to be used in the intensive therapy group was presented to the participating physicians. Within the first 6 months of the trial

patients in this group was seen every month and thereafter every 3rd month. The final HbA_{1c} level was reached after 36 months of follow-up. As mentioned, patients in the intensive group of the ACCORD study were in contact with the diabetes team every month throughout the follow-up period with the aim of rapidly reducing glycated HbA_{1c} levels. This setup ensured that the final HbA_{1c} level was obtained already within the first 4–6 months. Regarding microvascular complications it has long been known that a sudden lowering of longstanding hyperglycemia control can worsen retinopathy, especially in patients with previously known retinopathy in type 1 diabetes.[5,6] A similar phenomenon might exist for macrovascular complications. However, in that respect it is interesting that in the ACCORD study a nonsignificant trend toward a greater effect of intensive treatment on mortality among individuals with baseline HbA_{1c} >8% (vs. ≤8%) was observed, while the primary outcome (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) occurred significantly less often in the intensively treated subgroup among the subgroup with baseline HbA_{1c} ≤8%.[7]

Finally, since the ACCORD study was stopped before scheduled, lack of power regarding the combined macrovascular primary study endpoint precludes final conclusions on the role of very tight glucose control on this endpoint over longer follow-up periods. It is quite plausible, that the effect of glucose lowering therapy on cardiovascular disease may need longer time before becoming evident.

In conclusion, results from the ACCORD and ADVANCE studies do not give a definitive answer regarding the role of intensive glucose lowering therapy and mortality. Although disappointing results were seen on cardiovascular disease, it should be recalled that intensive glucose lowering therapy has marked effects on the reduction of microvascular complications[8], a result also seen in the ADVANCE study. However, the results once again emphasize the importance of intensified multiple risk factor intervention in patients with type 2 diabetes as seen in the Steno-2 study, since such an approach cuts the risk of both micro- and macrovascular disease as well as mortality with 50%.[9-11] Current guidelines already recommend goals very similar to the multiple treatment goals in the Steno-2 study and every effort should be made to achieve these. Regarding the specific goal for glycemic control both the International Diabetes Federation and the joint guidelines from the European Society of Cardiology and European Association for the Study of Diabetes recommends a HbA_{1c} goal of ≤6.5%.[12,13] This should still be the primary goal; however, caution is essential if this goal cannot be attained without frequent hypoglycemia, just as contraindications for the specific drugs used to lower blood glucose should be kept in mind.

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