Implications of Contemporary Clinical Trials

Effects of Intensive Glucose Lowering in the Management of Patients With Type 2 Diabetes Mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

Matthew C. Riddle, MD

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to test whether treatment targeting nearly normal glycemic control reduces the risk of cardiovascular events in type 2 diabetes mellitus. This aim was based on consistent epidemiological evidence that higher glucose and hemoglobin A1c (HbA1c) levels are associated with greater cardiovascular risk, together with inconclusive results from smaller and shorter interventional studies. All 10 251 participants in ACCORD were randomized to either a standard treatment strategy that targeted HbA1c levels between 7% and 7.9% or an intensive strategy that sought to attain an HbA1c <6.0%. With each strategy, investigators could prescribe any antihyperglycemic agent approved by regulatory authorities. The median HbA1c with the standard strategy was 7.5%; the intensive strategy achieved a median HbA1c of 6.4%. However, the intensive strategy was stopped after a median follow-up of 3.4 years, ~60% of that planned, because of 22% higher all-cause mortality. Participants previously using the intensive strategy were switched to the standard strategy and continued in the trial. The cardiovascular and microvascular effects after the full 5 years of randomized treatment have shed light on these issues.

Baseline Factors Associated With Risk During Intensive Treatment

As expected, various factors such as age and presence of comorbidities were associated with higher risk of death during randomized treatment. After adjustment for these factors, 3 baseline characteristics emerged as independent predictors of excess risk with the intensive strategy. Notably, a baseline HbA1c value >8.5% predicted 64% higher risk. History of taking aspirin (perhaps indicating perceived high cardiovascular risk) and self-report of having neuropathy (presumably reflecting microvascular injury) were also independent predictors.

Hypotheses About Postrandomization Factors

Proposed causes of excess mortality during use of the intensive strategy include hypoglycemia, rapid reduction of glucose or maintenance of near-normal levels, effects of drugs or drug combinations, and weight gain. Hypoglycemia has attracted the most suspicion. The incidence of first occurrence of hypoglycemic events requiring medical assistance was greater (3.14% yearly) in the intensive group than in the standard treatment group (1.03% yearly). However, as an adjudicated cause of death, hypoglycemia was uncommon in both groups (8% possible or probable with standard treatment, 11% possible or probable with intensive treatment) and considered a definite contributor to just a single death in the intensive group. In general, the risk of death was higher among individuals who had at least 1 episode of hypoglycemia requiring medical assistance (hazard ratio, 2.87 with standard treatment and 1.28 with intensive treatment). However, among those with a prior episode of severe hypoglycemia, the individuals in the intensive group had lower risk of later death than those in the standard group (hazard ratio, 0.55; 95% confidence interval, 0.31 to 0.99). With both treatment strategies, hypoglycemia requiring medical assistance was more frequent when HbA1c values were high than when they were low. Finally, hypoglycemia requiring medical assistance was more likely when participants in the intensive group achieved little reduction of HbA1c in the first 4 months of randomized treatment and less likely with larger early reductions.

The analyses of relationships between HbA1c and mortality have also produced surprising results. The well-known epidemiological relationship between glucose levels and greater risk of mortality has been confirmed in the whole ACCORD population. With 1% higher average HbA1c during randomized treatment, the risk of death was ~20% greater. This finding presents a paradox: greater risk with higher HbA1c yet higher mortality in the intensive group that was seeking and generally achieved lower HbA1c. The paradox has been (at least partly) resolved by analyses showing markedly different relationships between HbA1c and mortality with the 2 treatment strategies (the Figure). With the intensive strategy, the...
lowest risk of death was associated with lower levels of average \( \text{HbA1c} \). As average \( \text{HbA1c} \) increased from 6\% to 9\%, mortality risk increased steadily. The minority subgroup of individuals in the intensive group who had average \( \text{HbA1c} > 7\% \) accounted for the excess risk accompanying that treatment regimen. This interpretation was strengthened by another analysis showing that higher risk in the intensive group was associated with little reduction of \( \text{HbA1c} \) from baseline in the first 4 months or the first 12 months of treatment.

**Conclusions From Current Data and Remaining Questions**

To summarize, analyses from the ACCORD glycemia study confirm that higher levels of \( \text{HbA1c} \) generally predict higher risk of mortality in a population of people with type 2 diabetes mellitus selected for having high cardiovascular risk. They also show that an intensive glucose-lowering strategy, using treatment methods available at the time of the study, caused in the first 3 years a 22\% increase in deaths. This adverse outcome was associated with high \( \text{HbA1c} \) levels at baseline, and it occurred especially among individuals who attempted the intensive strategy but failed to reduce \( \text{HbA1c} \) much from their baseline levels and continued to have \( \text{HbA1c} \) levels >7\% while using this strategy. A contribution from severe hypoglycemia in the intensively treated group has not been confirmed.

These findings are helpful, but many questions remain. When evidence of the effects of intensive treatment on nephropathy, retinopathy, cognition, and various nonfatal cardiovascular end points after 5 years of follow-up becomes available, the short-term risk of death can better be weighed against these potential longer-term benefits. Still, it is worrisome that the underlying cause of excess mortality with intensive treatment remains unknown. Effects of specific drugs or of weight gain certainly might be involved and require more study. In addition, despite a lack of clear evidence for a causal role of hypoglycemia, there are reasons not to discard this hypothesis entirely. Hypoglycemia can cause cardiac ischemia or arrhythmia,\(^7\) plausibly mediated by secretion of catecholamines. In the intensively treated group in ACCORD, both higher risk of severe hypoglycemia and higher risk of death were associated with average \( \text{HbA1c} \) remaining >7\%. An association of greater risk of severe hypoglycemia with higher \( \text{HbA1c} \) has been reported in other studies\(^8\)\(^9\) and might reflect either physiological or behavioral characteristics of subgroups of patients. Finally, among participants who had at least 1 severe hypoglycemic event, minor hypoglycemia (which was more frequent with intensive treatment) was associated with lower risk of subsequent death.\(^5\) Repeated minor hypoglycemia has been reported to be protective against brain injury from subsequent severe hypoglycemia.\(^10\) Might “hypoglycemic preconditioning,” although associated with increased risk of severe hypoglycemia, protect against cardiovascular death resulting from severe hypoglycemia by reducing the catecholamine response\(^11\)? If so, were the individuals with \( \text{HbA1c} > 7\% \) using the intensive strategy at higher risk of death accompanying a severe hypoglycemic event not preceded by milder hypoglycemia? Because of the limitations of posthoc analyses, these complex questions may not be resolved with the ACCORD data, but they are worth asking because of their clinical implications.

**Practical Implications**

The ACCORD results pose specific questions for physicians in clinical practice. How can we identify those individuals with type 2 diabetes mellitus who may be at risk if they attempt an intensive glycemic treatment strategy? \( \text{HbA1c} \) >8.5\% on prior therapy appears to be a predictor of risk. A limited \( \text{HbA1c} \)-lowering response in the first 4 to 12 months of treatment may be another indicator, but a more objective way of defining this is needed. Moreover, the idea that a single \( \text{HbA1c} \) target is appropriate for all people with type 2 diabetes mellitus is being reexamined. The ACCORD results suggest that, in this case, one size does not fit all, at least with currently available therapies. Seeking an \( \text{HbA1c} \) of \( \leq 7\% \) for healthy patients with shorter duration of diabetes mellitus still seems appropriate, but for patients with a long duration of diabetes mellitus, established complications, and perhaps other risk factors, a higher target range might be defined. On this point, both further data and systematic review by advisory groups are needed.

**Acknowledgments**

This work was supported in part by the Rose Hastings and Russell Standley Memorial Trusts.

**Disclosures**

None.

**References**


Effects of Intensive Glucose Lowering in the Management of Patients With Type 2 Diabetes Mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial
Matthew C. Riddle

Circulation. 2010;122:844-846
doi: 10.1161/CIRCULATIONAHA.110.960138

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/122/8/844

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/