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

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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 will soon be reported. Meanwhile, debate continues as to why there was higher mortality with intensive treatment and the clinical implications. Several analyses of the data obtained during 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 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
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? HbA1c >8.5% on prior therapy appears to be a predictor of risk. A limited 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 HbA1c target is appropriate for all people with type 2 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.

**Practical Implications**

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**Disclosures**

None.

**References**


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