COMMENTS AND RESPONSES

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association

Response to Skyler et al.

Recently, international cardiovascular disease (CVD) and diabetes associations have published type 2 diabetes treatment guidelines based on the UK Prospective Diabtes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) (1,2), among others, recommending an A1C target of <7.0% for most patients. The evidence supporting this recommendation is ranked as level A—the highest possible (with evidence from multiple randomized trials/meta-analyses) (1). However, to our knowledge, the Kumamoto study of 110 Japanese patients is the only long-term type 2 diabetes investigation of intensive versus conventional control with clinical events as primary outcomes that has adopted this recommendation (3).

The UKPDS, ACCORD, ADVANCE, and VADT (or the Diabetes Control and Complications Trial for type 1 diabetes) used different targets (1,4), and meta-analyses have not addressed A1C targets. In clinical trials, participants can be randomized to a target A1C level but not to the level achieved. Hence, achieved A1C levels constitute observational data, thereby precluding inferences about causality, whereas the target levels, as part of the randomized treatment strategy, can support causal inferences concerning outcomes. Since the ranking of the A1C target of <7.0% as level-A evidence is based on a small number of patients in a single randomized study and on observational data (e.g., achieved glycemic levels) from most other randomized studies, this degree of confidence seems excessive to us.

However, the ADVANCE study of ~11,000 type 2 diabetic patients with high-risk of CVD demonstrated clinical benefits (reduced microvascular outcomes) with no harm (with respect to CVD or mortality) of intensive control (A1C target of ≤6.5%) versus conventional control (A1C target defined by local guidelines) (1). Preexisting CVD did not affect the conclusions. Despite employing different targets, with intensive control, the ACCORD (A1C target of <6.0%) and ADVANCE studies achieved a similar A1C (~6.5%). Therefore, differences in intensive control targets and/or unknown drug interactions may explain the mortality (safety) differences between the studies.

The ADVANCE study, with intensive control, found an ~2–3% higher risk of severe hypoglycemia, which is considerably lower than that found in ACCORD or the VADT (~15–20%) and lower than that in their conventional arms (~5–10%) (1). In fact, the conventional arm of the ACCORD study had an A1C target of >7.0%. Hence, using an A1C target of ≤6.5% (as in the ADVANCE study) rather than <7.0% might not per se increase the frequency of severe hypoglycemia.

Notably, in the ACCORD study, *1*) hypoglycemia was not significantly related to the excess mortality with intensive control; *2*) intensive control increased mortality irrespective of preexisting CVD; and *3*) in patients with preexisting CVD, intensive control had no effect on CVD (i.e., no harm). Hence, during intensive control, hypoglycemia did not explain the increased mortality and preexisting CVD did not adversely affect mortality or CVD risks (5).

In conclusion, there is little evidence to support the use of an A1C target of <7.0%. The safety of an achieved level might depend on the target level of A1C. The ADVANCE study suggests that targeting and achieving an A1C of ≤6.5% would be safe and beneficial for most type 2 diabetic patients. Significant hypoglycemia should always warrant consideration of aiming for less intensive control.

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