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 Lund and Vaag

We thank Lund and Vaag (1) for their interest in the statement on intensive glycemic control and the prevention of cardiovascular events written by the American Diabetes Association (ADA), the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA) (2). The consensus algorithm on management of type 2 diabetes referenced in their letter represents the expert opinion of its authors alone (3) and was not written in response to the cardiovascular disease trials; therefore, our response only deals with the ADA/ACCF/AHA statement (2).

The ADA has suggested an A1C treatment goal of <7% for most patients with diabetes since 1994. At that time, it was based on the Diabetes Control and Complications Trial (DCCT) findings but was later supplemented by the UK Prospective Diabetes Study (UKPDS) and Kumamoto findings, all of which focused on microvascular outcomes. The ADA has also stressed individualization of glycemic goals based on individual characteristics and preferences of patients. The AHA and ACCF have affirmed ADA recommendations in this area. The position statement (2) was an opportunity for the ADA, joined by representatives of the AHA and ACCF, to reevaluate its recommendations for glycemic control in light of the results of three studies: Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT).

It is true that very few of the randomized controlled trials (RCTs) have had an A1C target of <7% in their intensive glycemic control arm. Nevertheless, those who establish treatment guidelines are faced with the issue of translating resource-intensive research protocols into general clinical care recommendations. As such, the writing committees need to carefully weigh the potential benefits and risks of any intervention under consideration. Although the ADA/ACCF/AHA statement provided separate recommendations for the prevention of microvascular and macrovascular disease in patients with type 2 diabetes (due to disparate evidence regarding the benefit of intensive glycemic control for these end points), the micro- and macrovascular disease processes are frequently inseparable in clinical care, and each patient has a single glycemic target.

In regard to the macrovascular end points, the three recent large RCTs (ACCORD, ADVANCE, and the VADT) showed no evidence that aggressive glucose control reduces cardiovascular disease events in patients with type 2 diabetes. Moreover, the findings from ACCORD suggested a possibility of increased all-cause mortality in the intensive arm. Though this finding was not confirmed in other studies and the reasons for it remain unclear, it needs to be carefully considered when making broad recommendations regarding the intensity of glucose lowering. Reflecting the lack of benefit in regard to cardiovascular disease from three recent RCTs, and balancing it with recent data from UKPDS, the macrovascular recommendation from ACCF/AHA is of class IIb, which implies that the benefit/risk balance of intensive glucose control remains unclear.

In regard to microvascular disease, the ADA level-A recommendation (in this case the recommendation of an A1C <7% for most patients) can be based on clear evidence from multicenter RCTs or from supportive evidence from such trials. AHA and ACCF level-A evidence is characterized as sufficient evidence from multiple RCTs for a class I recommendation (e.g., the microvascular recommendation). This recommendation is based not only on the findings of Kumamoto et al. but also on achieved A1C levels of 7.0% from UKPDS (which was designed to target fasting glucose and did not prespecify A1C goals). This is more than merely observational evidence: it represents the levels achieved in those randomized to the intensive glucose-lowering arm—not a post hoc observation of all patients in the study. The ADVANCE study provided further evidence that more intensive glucose control reduces renal complications of type 2 diabetes.

Though the A1C target in ADVANCE was indeed <6.5% (rather than <7.0%), the writing group feels that changing the overall treatment recommendation to <6.5% from a long-standing recommendation of <7% simply based on the findings of ADVANCE is not a balanced approach. Intensification of glucose lowering is associated with a greater risk of severe hypoglycemia—the finding reinforced in all of the recent RCTs. Although Lund and Vaag suggest that the ACCORD study found no clear link between hypoglycemia and death, the randomized nature of these trials makes the proof of no causality nearly impossible. More data from ACCORD and the VADT are forthcoming and may clarify this issue. In the interim, the reduction in albuminuria seen in the intensive arm of ADVANCE (with target A1C <6.5%), which may take many years to translate into adverse patient outcomes, has to be balanced against the potential risks of more frequent severe hypoglycemia and the lack of benefit in terms of macrovascular events.

Our statement also expands on prior recommendations for individualized therapy. For some patients, more aggressive goals might be appropriate (e.g., an A1C <6.5%). The statement cites the ADVANCE microvascular findings as supportive evidence for this recommendation. Patients who have long life expectancy (hence, are likely to see microvascular benefits), no significant hypoglycemia history, and no established vascular complications would fit into this subgroup. In contrast, patients who are more likely to experience harm (e.g., those with a history of hypoglycemia) or who are unlikely to benefit from more aggressive therapy (those with ad-

vanced complications) might be candidates for even higher goals (e.g., the 7–8% goal of the standard arm of ACCORD).

In summary, we feel that the weight of available evidence and the risk-to-benefit ratio do not warrant changing the glucose control target to an A1C of <6.5% for the majority of patients with type 2 diabetes. For the ADA, this would be an intensification of our long-standing recommendation of <7.0%, and we did not feel that this was merited in the face of multiple recent RCTs that showed no benefit from intensive glycemic control in reducing macrovascular events—the most common and morbid complication of type 2 diabetes. This consensus was carefully vetted through peer review and was approved by the leadership of all three organizations (ADA, ACCF, and AHA). Future studies may offer additional data regarding the optimal A1C treatment targets in various patient subgroups. Until this information becomes available, our organizations continue to support an A1C goal of <7% as evidence based, safe, and achievable for the majority of patients with type 2 diabetes while continuing to support individualization of treatment goals based on patient characteristics and preferences.

JAY S. SKYLER, MD, MACP

From the University of Miami, Miami, Florida.
Corresponding author: Jay S. Skyler, jskyler@miami.edu.
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Acknowledgments— A list of potential conflicts of interest relevant to this article can be found in ref. 2.

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