

## CORRESPONDENCE



## Intensive Glucose Control in Type 2 Diabetes

**TO THE EDITOR:** In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (June 12 issue),<sup>1</sup> the intensive-therapy group differed from the standard-therapy group not only in the glycated hemoglobin level achieved but also in the number of drug classes prescribed to achieve it. It is plausible that in the subgroup of patients with a baseline glycated hemoglobin level of 8% or less who had a benefit with intensive treatment, the target glycated hemoglobin level was achieved with fewer drug classes than in the subgroup of patients with a higher baseline glycated hemoglobin level. Thus, one wonders whether the excess deaths in the intensive-therapy group occurred disproportionately among patients who required more drug classes. Furthermore, was the median glycated hemoglobin level among patients in the intensive-therapy group who died or had cardiovascular events similar to that in the rest of the group? Did the excess deaths in the intensive-therapy group occur in patients in whom the target glycated hemoglobin level was achieved or in those in whom the target was not achieved despite aggressive polypharmacy? Is it possible that instead of achieving a lower level of glycated hemoglobin, the aggressive polypharmacy that was necessary to control refractory hyperglycemia was associated with excess deaths?

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1. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.

**TO THE EDITOR:** The authors of the report on the ACCORD trial fail to emphasize that the observed increase in mortality with an intensive glucose-lowering strategy could have been related to the adverse effects of the drugs chosen rather than due to a lowering of the glycated hemoglobin level to 6.5%. Heavy use of rosiglitazone in the intensive-therapy group raises concern, despite the inability, claimed briefly by the authors, to statistically relate its use to the increased mortality. The fact that fluid retention, weight gain, and congestive heart failure, all potential adverse effects of rosiglitazone, developed in a higher proportion of patients in the intensive-therapy group supports such a possibility. Two meta-analyses have shown that the use of rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes.<sup>1,2</sup> It would be interesting to look at the outcomes separately in study participants taking rosiglitazone in both

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groups. The public, patients with type 2 diabetes, and physicians taking care of such patients need to be correctly informed in order to avoid the premature conclusion that normalizing glycated hemoglobin to 6.5% is harmful in high-risk patients with type 2 diabetes.

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1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71. [Erratum, *N Engl J Med* 2007; 357:100.]
2. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; 298:1189-95.

**TO THE EDITOR:** The ACCORD Study Group draws conclusions that are surprisingly different from those of the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) Collaborative Group, reported in the same issue.<sup>1</sup> One obvious difference between these two studies deserves analysis. The population of patients in the ADVANCE trial began and ended the study with a mean weight of 77 to 78 kg in all groups. Patients in the ACCORD trial started out with a mean weight of 93 kg (fully 15 kg heavier), and a large number of patients in each group gained weight during the trial. In fact, 14% of patients in the standard-therapy group and 28% in the intensive-therapy group gained more than 10 kg. This led to a significant difference in the weight outcomes of the treatment groups. Thus, a major risk factor was introduced disproportionately into the ACCORD trial. It would be of interest to see the ACCORD Study Group do a separate analysis comparing patients who did not have significant weight gain in each of the trial groups to see whether the conclusions hold. Or, conversely, was morbidity or mortality greater among the patients who had inordinate weight gain in each treatment group?

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1. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.

**TO THE EDITOR:** In the article by Patel et al. (the ADVANCE Collaborative Group), Table 1, which details the baseline characteristics of the two study populations, does not specify the type of blood-pressure medications the subjects were taking.

The incidence and progression of nephropathy in subjects with diabetes have been shown to be related to the type of blood-pressure medications being used to control hypertension, with angiotensin-converting-enzyme (ACE) inhibitors<sup>1,2</sup> and angiotensin-receptor blockers known to be renoprotective.<sup>3</sup> On the other hand, other hypertension medications such as amlodipine have not been beneficial in reducing the progression of microalbuminuria in subjects with diabetes, despite the similar blood-pressure control those drugs provide.<sup>4</sup>

The type of blood-pressure medication used also affects cardiovascular-related mortality and morbidity, especially in subjects with diabetes who have a history of vascular disease.<sup>5</sup> Since the specific class of hypertensive medications affects nephropathy and other end points measured in the study, documentation of their use in the two study groups and stratification would have made the study results more credible.

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1. Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. *J Am Soc Nephrol* 2006;17:Suppl 2:S153-S155.
2. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2005;4:CD004136.
3. Coronel F, Cigarrán S, García-Mena M, Herrero JA, Calvo N, Pérez-Flores I. Irbesartan in hypertensive non-diabetic advanced chronic kidney disease: comparative study with ACEI. *Nefrologia* 2008;28:56-60. (In Spanish.)
4. Yasuda G, Ando D, Hirawa N, Umemura S, Tochikubo O. Effects of losartan and amlodipine on urinary albumin excretion and ambulatory blood pressure in hypertensive type 2 diabetic patients with overt nephropathy. *Diabetes Care* 2005;28:1862-8.
5. Setoguchi S, Glynn RJ, Avorn J, Mittleman MA, Levin R, Winkelmayer WC. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008;51:1247-54.

**DR. BYINGTON AND COLLEAGUES REPLY:** The ACCORD glycemia trial was designed to determine whether targeting a glycated hemoglobin level of less than 6% reduced major cardiovascular out-

comes as compared with targeting a glycosylated hemoglobin level between 7 and 7.9% in patients with established type 2 diabetes, other cardiovascular risk factors or cardiovascular disease, and a glycosylated hemoglobin level of 7.5% or higher. A comprehensive strategy comprising lifestyle recommendations and all available classes of glucose-lowering drugs was used to target the two glucose levels. Because of the randomized design, the most appropriate conclusions from the ACCORD trial result from the comparison of these two comprehensive strategies. Whether one or another component of these strategies was responsible for the findings is certainly of interest and warrants exploration. However, because participants were randomly assigned to a comprehensive strategy and not any particular component of the strategy, exploratory analyses can only be hypothesis-generating.

The letters by Jenny-Avital, Luan and Nguyen, and Tobey all raise hypotheses that may account for ACCORD's glycemic findings. These and other possible explanations are being explored in multiple analyses to be submitted for careful peer review and publication. The common suggestion in these letters is for a more detailed presentation of analyses examining the possible cause (or causes) of the excess mortality observed in the ACCORD intensive-therapy group. As noted in our article, analyses attempting to determine the effects of interventional components on outcomes (such as mortality) are confounded by postrandomization characteristics of the participants or treatment changes. Such analyses must be conducted carefully and are challenging to interpret. Nonetheless, the ACCORD Study Group is very interested in these questions, and we are working diligently and systematically to publish our findings in great detail.

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**DR. PATEL AND COLLEAGUES REPLY:** Parashar raises concerns that differences in the use of various blood-pressure-lowering drugs between the inten-

sive-control group and the standard-control group of the ADVANCE trial might explain some of the observed effects on the study outcomes, particularly with respect to nephropathy. This was not the case. As would be expected in a randomized trial of this size, there were no differences in the use of such drugs between the randomized groups at baseline. This includes use of ACE inhibitors (43.1% of patients in the intensive-control group and 42.9% in the standard-control group), angiotensin-receptor blockers (5.5% and 5.4%, respectively), beta-blockers (24.3% and 24.7%), thiazide or thiazide-like diuretics (14.4% and 14.2%), and calcium-channel blockers (30.6% and 31.0%). By the end of the follow-up period, the use of such treatments remained similar between the intensive-control group and the standard-control group for ACE inhibitors (52.6% and 50.9%, respectively), angiotensin-receptor blockers (12.4% and 12.6%), beta-blockers (33.7% and 33.6%), thiazide or thiazide-like diuretics (4.3% and 5.1%), and calcium-channel blockers (36.9% and 37.4%). However, we would also contend that there is currently no clear evidence from randomized trials that particular classes of blood-pressure-lowering agents afford different levels of protection against macrovascular disease in people with diabetes.<sup>1</sup>

Tobey highlights differences in weight gain between randomized groups in the ADVANCE and ACCORD trials and speculates that these might account for some of the differences in the findings of the two studies. Overall, the strategy of intensive glucose control used in the ADVANCE trial was not associated with significant weight gain. However, although it may be reasonable to speculate that weight change may affect clinical outcomes, adjusted or stratified analyses based on postrandomization weight change are potentially highly confounded. We do not believe such analyses would meaningfully contribute to an understanding of the effects of differences in weight change on the occurrence of the study outcomes.

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1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165:1410-9.