Intensive therapy of type 2 diabetes (ACCORD trial)

(OCTOBER 2008)

TO THE EDITOR: I read with great interest Dr. Byron Hoogwerf's summary[1] of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[2] in your October issue.

I am curious as to your opinion, though. I previously e-mailed two other ACCORD investigators to ask if they planned to look at which subgroups were responsible for the higher death rate in the intensive-therapy group. They cannot get this data until after the lipid portion is unblinded next year.

The early release of data and discontinuation of one ACCORD arm is of concern but the data may shed light on the failure of previous trials. Muraglitazar was a failed dual peroxisome proliferator-activated receptor (PPAR) alpha and gamma agonist; it had outstanding effects on surrogate markers but was harmful regarding total mortality.[3] The same outcomes were seen in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: lower cardiovascular morbidity rate but higher total mortality rate,[4] prompting an exchange between Dr. Steven Nissen and me in *JAMA* in 2006.[5,6]

I think it would be prudent to evaluate the total mortality rate as well as cardiovascular morbidity in the study population receiving thiazolidinediones alone, fibric acid alone, both together, or neither. The group of patients most likely to receive both agents (those who are obese, with metabolic syndrome or diabetes) is a very large population. If the data analysis confirms that dual PPAR inhibition raises total mortality rates, that information should be made public as soon as it is available. It may be prudent to review those data before official publication in 2009.

DAVID M. NAJMAN, MD
Assistant Professor of Medicine, Northwestern University
Director, Lipid Clinic, Northshore University Health System
Evanston, IL

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TO THE EDITOR: I certainly enjoyed Dr. Byron J. Hoogwerf's excellent summary article regarding intensive therapy of type 2 diabetes. I was concerned, however, about the sentence in his last paragraph stating that "any strategy that lowers glucose and is not associated with a risk of hypoglycemia and does not cause excessive weight gain should be considered appropriate in patients with type 2 diabetes." This statement begs the question: What is excessive weight gain?

In view of the known adverse effects of obesity on hypertension, lipid disorders, and insulin resistance, how can any weight gain be beneficial? Is there any evidence that lowering glucose has any benefit when it is associated with weight gain?

JOHN W. DRAKE, MD
Oklahoma City, OK

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IN REPLY: Dr. Najman's concern about reasons for the slight mortality increase in the intensively treated group in ACCORD[1] resonates with all of the ACCORD investigators and clinicians. However, several features of the ACCORD trial should provide reassurance about his concerns.

At the time of protocol development, it was recognized that the complexity of the protocol was such that some issues, including medication combinations, might generate safety

concerns.[2] The ACCORD trial—like all appropriately designed large clinical trials—has a data safety and monitoring board. The ACCORD data safety and monitoring board is composed of people with extensive experience in the conduct and analysis of clinical trials. Among its roles are ongoing evaluation of the conduct of the trial (to ensure adherence to the protocol), determination of whether the trial has achieved efficacy outcomes (based on predetermined stopping rules), and judgments as to whether there are any safety concerns. The board may request any analyses it deems necessary for the safe conduct of the trial. The board meets regularly and reports regularly to the National Heart, Lung, and Blood Institute (NHLBI) project office.

The ACCORD data safety and monitoring board has been very attentive to issues that may have been of concern during the course of the trial. Most notably, when the report by Drs. Nissen and Wolski about rosiglitazone (Avandia) was published,[3] the board requested interim analyses of the ACCORD data for their review. It reported that rosiglitazone use in the ACCORD trial was not associated with a risk of increased cardiovascular events or death. The fact that they recommended to the NHLBI that the intensive glucose arm be closed early also attests to their care in ensuring the integrity of the ACCORD trial and the safety of each study participant.

Although the details of the board's discussions are not made available to investigators (or to the public), I am quite certain that the concern about the combination of PPAR alpha and gamma agonists is on their radar screen. And in the absence of safety concerns from the ACCORD data safety and monitoring board, it would be inappropriate to report any analyses to address the question raised by Dr. Najman prior to the closure of the lipid arm in ACCORD.

Dr. Drake raises a question for which there is no easy answer. We do not know how much weight gain actually contributes to coronary heart disease risk and mortality in a group of patients whose risk factors are otherwise well treated. Weight gain is clearly associated with increasing blood pressure, more adverse lipid profiles, and probably increased nontraditional risk markers, including high-sensitivity C-reactive protein and plasminogen activator inhibitor-1. The former risk factors can be treated with additional medication, and the effects of the latter are uncertain. Thus the writer raises an excellent question, but one that does not readily lend itself to a clearly quantifiable answer for "how much weight gain is too much?"

BYRON J. HOOGWERF, MD
Eli Lilly and Company
US Endocrinology-Diabetes Care
Principal Investigator
(Cleveland Clinic Site)
ACCORD Study Group

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