

Intensive glyceemic control arm of accord stopped prematurely

The ACCORD trial (Action to Control Cardiovascular Risk in Diabetes)¹ is a National Heart, Lung, and Blood Institute (NHLBI) study planned to investigate the effects of three different therapy strategies all aimed at reducing the increased morbidity-mortality in type 2 diabetes mellitus: intensive treatment of hyperglycemia,² hypertension, and lipid disorders. ACCORD is a North American (USA and Canada) randomized, multicenter (77 centers) trial, with a double 2X2 factorial design. 10251 middle aged or older patients with high vascular risk were included in the intensive glyceemic control arm. Recruitment was completed in May 2005, and the end of the study was planned for June 2009. However, the intensive glyceemic control arm was stopped prematurely in February 2008, due to a higher mortality rate in the patients included in the intensive group.³

The purpose of the intensive glyceemic control arm of ACCORD was to answer the question of whether an HbA1c goal of <6.0% is more effective at reducing the incidence of cardiovascular events than an HbA1c goal of 7.0%-7.9%. In this trial, a therapeutic strategy - and not a specific class of antidiabetic drugs - was tested. According to a predefined step by step strategy, patients received antidiabetic oral agents and/or insulin from a formulary of drugs, representing all the available classes of antidiabetic agents.² At inclusion, the ACCORD population was 61.4% male, had a mean age of 62.2 years, and included 64.8% white, 19.3% black, and 7.2% Hispanic patients. Mean diabetes duration was 10 years. The mean HbA1c value was 8.3% (median 8.1%). The diabetic status of the patients corresponded with secondary prevention in 35.2% of cases.

The intensive glyceemic control arm of ACCORD was stopped prematurely 18 months before the end of study. The reason for this was an increase in the number of all-cause deaths in the intensive group compared with the standard group (257 vs 203): 14/1000/year in the intensive arm, compared with 11/1000/year in the standard control arm; ie, excess deaths of 3/1000/year.

Only limited data concerning the premature end of ACCORD are currently available.³ The median HbA1c value was 6.4% in the intensive group, compared with 7.5% in the standard group (1.1% difference). Globally, the death rate in the two groups was lower than expected from previous studies (around 50/1000/year). There was a trend toward a lower incidence of cardiovascular events in the intensive group (around 10%), but mortality and sudden death rates were higher in this group.

No definitive explanation has been given by the Steering Committee of ACCORD. Extensive analysis of the results is ongoing, with a presentation of the results scheduled for the ADA San Francisco Meeting in June 2008.

Different hypotheses have been proposed, including the simple effect of chance, an adverse reaction to a specific drug or an association of drugs, a deleterious effect of a too severe decrease in blood glucose levels in such an at-risk population, or an effect of stress induced by intensive treatment and the self-monitoring regimen.

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References:

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2. Gerstein HC, et al. *Am J Cardiol.* 2007;99:34i-43i.
3. National Heart, Lung, and Blood Institute. ACCORD telebriefing prepared remarks. February 6, 2008. Available at: <http://www.nhlbi.nih.gov/health/prof/heart/other/accord/index.htm>. Accessed 30 April 2008.

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