

## Multifactorial Intervention and Mortality in Type 2 Diabetes

**TO THE EDITOR:** In their article on aggressive multiagent treatment of risk factors for diabetic complications, Gæde et al. (Feb. 7 issue)<sup>1</sup> comment that there were no differences in smoking status between the intensive-therapy and conventional-therapy groups. Because smoking is such an important and preventable cause of diabetic complications, it would be important to know the actual rates of smoking in the two study groups, whether smoking-cessation treatments were provided in either group, whether these interventions were similar in the two groups or more intensive in the intensive-therapy group, and whether there were any differences in the percentages of smokers who were able to quit. To achieve the best possible outcomes, aggressive tobacco-cessation treatment should be a core component of intensive diabetes care.

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1. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580-91.

**TO THE EDITOR:** Reduction of glycosylated hemoglobin values to the range of 7.0 to 7.9% has been associated with reduced cardiovascular events in both type 1 and type 2 diabetes.<sup>1</sup> A large study with a goal of lowering glycosylated hemoglobin levels to less than 6.0% was recently stopped because of higher mortality in the group of patients randomly assigned to receive strict blood glucose control.<sup>2</sup> The median glycosylated hemoglobin level was 6.4% in the strict-control group and 7.5% in the standard-care group. Although an increase in cardiovascular events has not been observed in the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial, the goal for glycosylated hemoglobin was less than 6.5%, not less than 6.0%, as in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. A reduction in the low-density lipoprotein cholesterol level to 83 mg per deciliter, a reduction in blood pressure to 131/73 mm Hg, and an average glycosylated hemoglobin level of 7.9% after the first 8 years of the study had widespread cardiovascular benefits. The improved lipid levels and blood pressure seem to

be the most important factors for reducing cardiovascular risk. Did Gæde et al. observe any association between the number of hypoglycemic events and the number of cardiovascular events?

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1. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353:2643-53.

2. Action to Control Cardiovascular Risk in Diabetes. ACCORD study announcement. (Accessed April 22, 2008, at <http://www.accordtrial.org/web/public/index.cfm>.)

**THE AUTHORS REPLY:** We have previously published results regarding lifestyle interventions in the Steno-2 Study.<sup>1</sup> At baseline, 40% of patients in the intensive-therapy group, as compared with 35% in the conventional-therapy group, were smokers. In the intensive-therapy group, structured smoking-cessation programs with consultations in groups of up to 14 patients (spouses included) were carried out throughout the follow-up period. Nicotine substitution was offered without cost to all participants. No structured programs were offered to the patients in the conventional-therapy group. At the end of the 7.8-year intervention trial, six patients in the intensive-therapy group had stopped smoking, as compared with five in the conventional-therapy group, and none of the patients in the conventional-therapy group had participated in any structured program. During the observational part of the study, there was a further decrease in the number of smokers in both groups; 22% of patients in the intensive-therapy group were smokers at the end of follow-up, as compared with 18% in the conventional-therapy group. However, these numbers are blurred by the large number of deaths among participants. We agree with Dr. Schroeder that smoking cessation is of utmost importance in the treatment of diabetes. Yet even structured smoking-cessation programs, as used in the Steno-2 Study, appear to achieve, at best, modest results. A more efficient approach, which might benefit the larger community, not only people with type 2 diabetes, might be to increase bans on smoking in public areas.<sup>2</sup>

Dr. Tayek points out the potential risk of an association between hypoglycemic events and mortality. We did not see such an association in the Steno-2 Study. On the contrary, a significant association between symptomatic hypoglycemia and reduced risks of both total and cardiovascular-related deaths was observed in the conventional-therapy group. A nonsignificant trend was seen in the intensive-therapy group. This was the case even for a reduction in total mortality among patients with major hypoglycemic episodes ( $P=0.075$ ).

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1. Gæde P, Beck M, Vedel P, Pedersen O. Limited impact of lifestyle education in patients with Type 2 diabetes mellitus and microalbuminuria: results from a randomized intervention study. *Diabet Med* 2001;18:104-8.
2. Cesaroni G, Forastiere F, Agabiti N, Valente P, Zuccaro P, Perucci CA. Effect of the Italian smoking ban on population rates of acute coronary events. *Circulation* 2008;117:1183-8.

## Iron-Overload–Related Disease in *HFE* Hereditary Hemochromatosis

**TO THE EDITOR:** The report by Allen et al. (Jan. 17 issue)<sup>1</sup> on iron-overload–related disease in patients with *HFE* hereditary hemochromatosis states that among men, the clinical penetrance among *HFE* C282Y homozygotes was 28.4%. Our study showed

that only about 2% of male C282Y homozygotes had full-blown clinical disease.<sup>2</sup> We are disappointed that the authors still suggest that our results were biased because we excluded patients with a prior diagnosis of hemochromatosis, even after

**Table 1. Characteristics of Male *HFE* C282Y Homozygotes.**

Characteristic or Diagnosis	Male <i>HFE</i> C282Y Homozygotes in the Study by Allen et al. <sup>1</sup>	Male <i>HFE</i> C282Y Homozygotes in the Study by Beutler et al. <sup>2</sup>	P Value
	<i>no. (%)</i>		
Total	74	75*	
Iron overload†	27 (36.5)	18 (24.0)	0.09
Hepatocellular carcinoma	2 (2.7)	0	0.25
Cirrhosis	2 (2.7)	1 (1.3)	0.18
Fibrosis (grade 1–3)	10 (13.5)	Not determined	
Elevated alanine aminotransferase (>40 IU/liter) or aspartate aminotransferase (>45 IU/liter)	6 (8.1)	7 (9.3)‡	0.99
Abnormal metacarpophalangeal joints	5 (6.8)	0§	0.03
Previous diagnosis of hereditary hemochromatosis as a result of symptoms that prompted an evaluation, not otherwise specified	11 (14.9)	Not determined	
None of the above diagnoses	6 (8.1)	11 (14.7)	0.30

\* The total number includes four male C282Y homozygotes identified after publication of the study results.

† Iron overload was defined as elevated liver iron concentrations or serum ferritin concentrations higher than 1000 ng per milliliter in the study by Allen et al.<sup>1</sup> and serum iron concentrations higher than 1000 ng per milliliter in the study by Beutler et al.<sup>2</sup> In the study by Allen et al., one female homozygote was included in the published diagnostic breakdown.

‡ Follow-up for up to 8 years has shown no progressive increase in liver-enzyme levels with aging among homozygotes and no significant effect of phlebotomy on these levels.

§ In a subgroup of homozygotes examined specifically for this symptom, 3 of 16 (18.8%) had metacarpophalangeal joint pain, none of whom had ferritin levels above 1000 ng per milliliter.