

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

TO THE EDITOR: The report by Allen et al. (Jan. 17 issue)¹ 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.² 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. ¹	Male <i>HFE</i> C282Y Homozygotes in the Study by Beutler et al. ²	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.¹ and serum iron concentrations higher than 1000 ng per milliliter in the study by Beutler et al.² 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.

we showed them that the results were unaltered without this exclusion.³ Moreover, contrary to their assertion, all our patients were examined by a physician.

In reality, when examined side by side, our data are quite similar (Table 1) and resemble those in two other larger studies.^{4,5} The apparently high penetrance in the study by Allen et al. results from applying very liberal criteria in defining clinical disease. For example, the vague category of “diagnosis by a physician owing to symptoms associated with hereditary hemochromatosis” could well include patients with commonplace symptoms such as fatigue, which are then attributed, without proof, to iron overload.

Moreover, bias that increases symptoms attributed to hemochromatosis is introduced by not correcting for nonhomozygotes who have the same symptoms.

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TO THE EDITOR: The question concerning the penetrance of homozygous *HFE* C282Y alleles, addressed in the report by Allen et al. and other reports,^{1,2} has been confused with expressivity, the variability of the penetrant trait. The proportion of C282Y homozygotes with evidence of the trait of hepatic dysfunction is separate from the degree of severity of that dysfunction. Few would disagree that the abnormal biochemical, clinical, and histopathological findings among homozygotes are on a continuum of hepatic stress responses, with dysfunction and tissue destruction probably representing progressive hepatic injury. The question for clinicians is whether these findings lead to excess morbidity or mortality. In this study, the number of heterozygotes was lower than

predicted if they were in Hardy–Weinberg equilibrium; is there an age-related depletion of C282Y homozygotes? Allen et al. report no hepatic insufficiency or overall excess mortality associated with homozygosity. Are these findings owing to the very high rate and amount of blood donations or venesections that the authors report among homozygotes, or do they reflect a relatively benign natural history for C282Y homozygosity?

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THE AUTHORS REPLY: Waalen and Beutler highlight the point that in C282Y homozygotes, the definition of clinical disease (“clinical penetrance”) continues to be keenly debated. They confuse “serious disease” with iron-overload–related disease. In our study, the C282Y homozygous men with documented iron overload were significantly more likely to have objective disease associated with hereditary hemochromatosis (21 of 27 men, 78%) than the C282Y homozygous men without evidence of iron overload (2 of 15, 13%; $P < 0.001$).

Our estimate of the prevalence of iron-overload–related disease among homozygotes was based on a reduced list of hemochromatosis-associated signs and symptoms and included only objective measures of disease (including examination by a physician who was unaware of the *HFE* genotype and liver biopsy, neither of which were performed by Beutler and colleagues), in addition to the presence of iron overload as defined by Whitlock et al.¹ Our study showed a significantly higher prevalence of histologic liver damage than that reported by Beutler and colleagues (in 14 of 74 men vs. 1 of 75, $P < 0.001$), although our estimate is conservative, since not all homozygotes consented to undergo liver biopsy. The observed proportion of C282Y homozygotes with these objective disease symptoms remains an unbiased estimate of the population prevalence, even though these same symptoms were less prevalent among nonhomozygotes in our sample.

Although according to our definition of iron-overload–related disease, we included the 12 symptomatic homozygotes in whom the diagnosis was

made by a physician, all but 5 of them had other symptoms of hereditary hemochromatosis that would have independently met the study criteria for disease related to iron overload. Furthermore, of 10 male homozygotes with varying levels of iron overload but without symptoms in whom the diagnosis was made during the study period because of elevated iron values, cascade screening, or other reasons, 9 underwent therapeutic venesection to prevent progression to disease.

In response to Rienhoff, we cannot be sure that there was not an age-related depletion of homozygotes before the study. Although we are certain of the genotype of the 203 homozygotes after confirmatory testing, we may have underestimated the proportion of C282Y heterozygotes in our cohort of 31,192 participants because of technical

challenges of genotyping stored samples. The high rate of blood donation among our study participants may have abrogated the degree of iron loading found in C282Y homozygotes.

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Catheter Ablation in Patients with ICDs

TO THE EDITOR: We strongly support the rationale for ablation of ventricular tachycardia to reduce implantable cardioverter-defibrillator (ICD) therapy, described by Reddy et al. (Dec. 27 issue),¹ but would caution that risk stratification is essential to identify the subgroups of patients who would truly benefit from ablation in this setting. Ablation is time-consuming and technically challenging, with potentially significant complication rates.² In addition, there is evidence that the clinical presentation can be used to stratify the risk associated with ICD therapy.³⁻⁵ It is therefore unfortunate that the article by Reddy et al. omits both the procedural and the clinical details that would provide readers with insight into the central questions of resource utilization and the risk-benefit ratio. Since patients with ICDs have protection against lethal ventricular arrhythmias, prophylactic substrate ablation alone would not be expected to influence mortality. Therefore, preventive ablation should be provided only in appropriate subgroups.

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TO THE EDITOR: In the editorial accompanying the report by Reddy et al., Estes¹ makes a recommendation against the use of prophylactic catheter ablation to prevent ICD therapy in patients with ischemic heart disease. Although I agree that catheter ablation should be limited to patients with recurrent ventricular arrhythmias, one should keep in mind that the only alternative in this population is treatment with antiarrhythmic drugs. However, the long-term safety of such a therapeutic strategy, which usually relies on amiodarone for its superior efficacy in preventing shocks, as compared with other agents,² has not been established. On the contrary, a recent study showed an increase in mortality among patients with an ICD who were treated with amiodarone.³ The finding,