previous reports that showed the lowest frequency for the e4 allele in Southern European populations (2–6). The low frequency of the e4-frequency allele among Mediterraneans has been linked with a decreased risk of CAD in these populations, compared to Northern Europeans, who have the highest e4-frequency and the highest rate for CAD in Europe.

In accord with this, we did not find a significant difference for the Apo E gene and genotype frequencies between patients and controls, suggesting that the e4 allele is not a strong risk factor for early CAD in our population. The role of Apo E genotypes in the risk of CAD has been analyzed previously (7,8).

For the e4-allele, a significantly increased frequency in patients compared to healthy controls has been described in some but not all studies. These discrepancies could be partly attributed to the fact that these studies analyzed different populations worldwide, and the e4-allele could be a risk factor in association with other genetic or environmental factors.

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REPLY

We appreciate the comments of Batalla et al. concerning our paper on premature coronary artery disease (CAD). The authors share with us their data on young adults admitted with acute coronary syndrome. They also provide follow-up information in the subgroup with normal cholesterol compared to those with abnormal cholesterol levels as defined by the ratio of total cholesterol to high density lipoprotein levels. There are some similarities between their data and ours; however, major differences exist. Similar features include the fact that both studies evaluated young adults age 50 years or younger. Second, both populations were high risk, with high rates of categorical risk factors. For instance, the rate of smoking was 73% in their study compared to 75% in our group. The rate of hypertension was 36% and diabetes mellitus was 9% in Batalla et al., which is similar to the 39% and 12% in our study for those two conditions, respectively.

Hypercholesterolemia was 77% in their report. The rate of hypercholesterolemia was 46% in our report, but the two studies used different definitions. A comparison between the two studies is limited by major differences in methodology and incomplete data provided by the authors. First, their report involves exclusively male subjects, whereas as many as 30% of our population were young women. Second, their analysis was done by comparing two groups based on cholesterol levels. We, in contrast, compared two groups based on irrefutable evidence of significant CAD. Furthermore, they do not specify the time period over which the data was collected. For this reason we do not know the frequency of admissions for premature CAD. Next, what percent does this represent for admissions of acute coronary syndrome?

We commend the authors for providing follow-up information on outcomes. In their report, after 32 months’ follow-up there were no differences in outcome between those with abnormal compared to normal cholesterol. They conclude that the absence of differences in outcomes represents a lack of benefit of low cholesterol in young adults with high rates of smoking. This interpretation is similar to an earlier report by Jee et al. (1) in subjects without previous CAD. The suggestion that low cholesterol does not confer a benefit for secondary prevention in young adults has important clinical implications. There are, however, other possible explanations. This was an observational study that did not consider the effect of treatment. It is possible that the lack of outcome differences may be attributable to some treatment benefit in the group with high cholesterol who were treated according to current guidelines. This actually proves the merit of guidelines for secondary prevention.

Finally, a secondary explanation concerns the small sample size. With a small sample size in each group it is possible that one would need a much longer duration of follow-up to appreciate differences. We do agree that, in young adults with multiple cardiovascular risk factors, the best strategy to reduce recurrent events in the short term should be based on managing all

Mild Hypercholesterolemia and Premature Heart Disease

In a recent study published in the Journal by Akosah et al. (1), the investigators found that the presence of borderline or mild hypercholesterolemia has significant effects on the development of premature coronary heart disease.

In this way, a group of 229 male patients <50 years of age (mean age 43 ± 5 years), who were admitted to our Coronary Care Unit as a result of an episode of coronary disease were prospectively studied. During the acute phase and by means of a structured questionnaire, the presence of smoking habits, hypertension, diabetes and dyslipemia were recorded. A physical examination and fasting analysis were also done. Due to clinical instability or persistent myocardial ischemia, 132 patients underwent a cardiac catheterization. In accordance with a previous report (2) we considered as normolipemia a total cholesterol/HDL cholesterol ratio (Tchol/HDL) ≤5. Two groups were established on this basis. To determine new coronary events, a mean follow-up of 32 ± 13 months was carried out. For statistical analysis, the chi square test and Fisher exact test were applied.

Our study was observational and did not suppose any intervention in the treatment. In the acute phase we found that 160 patients (73%) were smokers; 84 (36%) presented arterial hypertension; 21 (9%) had diabetes; and 181 (77%) had dyslipemia. In the follow-up, 45 patients (20%) retained smoking habits; 76 (34%) had arterial hypertension; 22 (10%) had diabetes; and 172 (75%) had dyslipemia.

The distribution of coronary lesions in the patients who underwent a cardiac catheterization were: normal coronaryography, 13 patients (10%); one vessel, 49 patients (37%); two vessels, 42 patients (32%); and three vessels, 28 patients (21%).

No differences were found in the prevalence of smoking habits (93% of our patients were smokers) and diabetes in either group (Tchol/HDL ≥5 vs. Tchol/HDL <5) (3).

Nor were there any differences in the appearance of angina, myocardial infarction, heart failure, mortality and the need for coronary revascularization in the follow-up period. Significant data are shown in Table 1.

We concluded that our patients, who were younger than 50 years of age, with ischemic heart disease, and who showed a Tchol/HDL ratio ≤5, present less prevalence of hypertension and show more frequently an absence of significant coronary lesions in comparison with those patients with an altered lipid profile. Furthermore, no additional benefits were found in relation to new coronary events (fatal and nonfatal). We interpret that this lack of benefit might be due to the high percentage of smokers in both groups. Finally, our data are coincident with those reported previously (4), showing that a normal lipid profile does not confer additional benefit to smokers.

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REPLY

Batalla and colleagues found in a sample of 220 Spanish men with coronary heart disease that frequencies of epsilon43 and epsilon44 genotypes did not differ from those among 200 age-matched controls. In contrast, we observed in the Danish population (by comparing genotype frequencies in 693 male patients with those among 4,129 men sampled from the general population) that the epsilon43 and epsilon44 genotypes compared with the wild-type epsilon33 genotype in men predicted 40% and 60% increases in risk of ischemic heart disease, respectively (1).

It is well established that there is a north-to-south decreasing gradient of the epsilon4 allele frequency throughout Europe (2,3). This is exemplified by an epsilon4 relative allele frequency of 17% in Spain versus 8% in the Spanish population, as demonstrated by Batalla et al. We agree that the lower frequency of the epsilon4 allele in Southern versus Northern Europe may...