total testosterone concentrations.[2] Guidelines on the evaluation of male hypogonadism also suggest measurement of free testosterone levels in men with total testosterone levels that are near the lower limit of the normal range or those with conditions such as obesity that might affect levels of sex hormone–binding globulin.[3] Therefore, we wonder why the free testosterone level was not considered as an inclusion criterion and whether the findings of the trials differed according to baseline concentrations of free testosterone or sex hormone–binding globulin.

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THE AUTHORS REPLY: Perls and Stavropoulos et al. comment that the Testosterone Trials were not designed to determine the risk of testosterone treatment. Our trials were designed to implement the recommendation of the Institute of Medicine that trials of efficacy were needed before it could be determined whether a trial of risk was justified.[1]

Perls also notes that many participants in our trials were obese. Because obesity is common in the United States, the results should be generalizable to men 65 years of age or older who have a low testosterone level. In spite of obesity, the free testosterone level in participants was also low, and testosterone treatment resulted in both symptomatic and objective benefits.

Stavropoulos et al. also ask about the effect of phosphodiesterase type 5 inhibitors on the sexual-function results. Fewer than 10% of men in the trials received phosphodiesterase type 5 inhibitors, and this rate was well-balanced between the two study groups, so we are not able to compare outcomes between the two groups.

Mata et al. suggest that targeting relief of symptoms would have been better than targeting a serum testosterone concentration. The goal of the Testosterone Trials was to determine whether increasing the serum testosterone concentration to within the normal range for young men would reduce both symptoms and objective deficiencies. We did not want to increase the serum testosterone level above normal because of the concern that doing so would increase risk.

Laurent et al. propose that the level of low free testosterone, rather than the level of total testosterone, should have been the basis for inclusion in the Testosterone Trials. As shown in Figure S2 in the Supplementary Appendix of our article (available with the full text of the article at NEJM.org), median serum free testosterone levels were less than half of the median of the normal level at baseline and they more than doubled during treatment; this is similar to the pattern for total testosterone.

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Aspirin before Coronary Artery Surgery

TO THE EDITOR: The title of the article by Myles et al. (Feb. 25 issue)[1] ("Stopping vs. Continuing Aspirin before Coronary Artery Surgery") indicates uncertainty about discontinuing aspirin before coronary-artery bypass grafting (CABG). However, the trial, Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS), does not address that uncertainty. All patients discontinued aspirin at least 4 days before surgery, and risks of perioperative complications among patients who

started aspirin immediately before surgery were compared with risks among patients who started aspirin after surgery. Furthermore, the factorial design in which some patients were assigned to receive tranexamic acid precluded assessment of aspirin-related bleeding in half the patients who received aspirin.

Our additional concerns about this trial include the use of enteric-coated aspirin, which has delayed and unpredictable absorption,[2] and the 100-mg dose of aspirin, which is lower than the recommended loading dose for patients with an acute condition.[3] Also, the definition of myocardial infarction changed from the definition that is currently accepted[4] to one that requires elevations in enzyme levels that are less marked than those recommended for patients after CABG[5] (the composite outcome was twice the rate predicted on the basis of earlier studies, and almost 75% of the patients who reached the composite outcome had myocardial infarction).

The randomized, double-blind design and large planned sample size were major advances over earlier, less rigorous designs.[6] Unfortunately, with the serious design flaws in this trial, the negative result does not resolve clinical uncertainty about whether patients should discontinue aspirin before CABG.

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TO THE EDITOR: The ATACAS trial by Myles et al. shows neither benefits nor disadvantages of a single dose of aspirin 1 to 2 hours before elective CABG in patients after aspirin has been discontinued for at least 4 days. Rates of thrombotic and bleeding complications were similar among patients who received aspirin and those who did not.

Unfortunately, the study design does not answer the question of whether it is best to stop or continue aspirin in patients undergoing CABG, since the influence of the "rebound phenomenon" after discontinuation of aspirin is not quantified.[1] The occurrence of the rebound phenomenon is hinted at by the unusually high rate of postoperative myocardial infarction (14.8%).

Furthermore, with the current emphasis on postoperative events, the preoperative risks of discontinuing antiplatelet drugs remain to be elucidated. Discontinuation of antiplatelet therapy is not without risks,[1] especially among patients with a recent acute coronary syndrome.[2] We were surprised that 7.5% of the patients in the trial had had a recent myocardial infarction, and most had stopped taking an antiplatelet drug at least 4 days before CABG.

The dilemma regarding continuation or discontinuation of aspirin before CABG remains to be solved. A trial in which patients are randomly assigned to either continue or discontinue aspirin 5 to 7 days before surgery, with assessment of both preoperative and postoperative events, may be more appropriate than the method used in the trial by Myles et al.

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THE AUTHORS REPLY: The concern about our title expressed by Alkhodair and Cairns overlooks the practical aims of the trial in that the reason pa-

tients were asked to discontinue aspirin before surgery was because of the perceived bleeding risk during and after surgery. That is, bleeding risk was not associated with aspirin until the actual surgery. We found that treatment with aspirin at a single dose of 100 mg before surgery did not pose any significant bleeding risk. Hence, there is no reason for patients to discontinue aspirin before coronary artery surgery because of this concern. Tranexamic acid is an antifibrinolytic drug that may or may not reduce aspirin-related bleeding; an evaluation with our factorial design is under way.

Enteric-coated aspirin may have less reliable absorption than an immediate-release formulation. However, enteric-coated aspirin is commonly used and has clearly been shown to be effective in patients with acute coronary syndromes.[1] Patients with ST-elevation myocardial infarction are different from those undergoing coronary artery surgery; the latter have a much higher bleeding risk and there is less urgency to induce platelet inhibition. The same guideline highlighted by Alkhodair and Cairns[2] recommends a preferred maintenance dose of aspirin as low as 81 mg daily, and it is with this dose that most patients present for surgery.

The universal definition of postoperative myocardial infarction was used in our trial, and the same expert group that created that definition included isolated markedly elevated troponin levels as being sufficient to diagnose myocardial infarction.[3] If we remove the latter events from our results, we lose 17 myocardial infarction events in the aspirin group and 15 myocardial infarction events in the placebo group; this reduces the myocardial infarction event rate by only 1.5 percentage points, and the point estimate of an aspirin effect remains unchanged (risk ratio, 0.94). An isolated but marked elevation in the troponin level after CABG is prognostically important.[3,4]

We accept the observation by Li et al. that our study design cannot quantify the influence of the aspirin rebound phenomenon, but this does not explain the high rate of postoperative myocardial infarctions reported in our trial. Troponin surveillance has greater sensitivity than creatine kinase–myocardial band in detecting small myocardial infarctions.[3]

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Incidence of Dementia over Three Decades in the Framingham Heart Study

TO THE EDITOR: Satizabal et al. (Feb. 11 issue)[1] report a steady decline in the incidence of dementia during the past three decades, represented by 5-year epochs, among participants in the Framingham Heart Study. We suspect that a statistical bias, truncation by death, might to some extent contribute to this finding. Each epoch included participants who were 60 years of age or older and dementia-free at the start of the study; participants who were still dementia-free at the end of an epoch could be included in the following epoch. In their analysis, in each epoch, data for participants were censored at the last date they were known to be dementia-free or at the date of death. Because of discrete follow-up visits, death could have precluded the observation of the onset of dementia, a factor that is known to result in an underestimated incidence of dementia[2] and bias in Cox model estimates.[3,4] This factor was also pointed out in the recent guidelines of the Methods in Longitudinal Research on Dementia (MELODEM) Initiative.[5] Over time, truncation by death bias gets even larger, which cannot be accounted for in age-adjusted estimates. To judge this problem, it would be in-