respect to the discontinuation of aspirin, the transfusion of platelets, and the use of antifibrinolytic therapy — all of which are associated with worsened morbidity. Nor did isolated group differences confound our findings. In addition, as Topol elegantly states, we should not discount the compelling experiences with aspirin therapy in at-risk medical patients.

In conclusion, we are left with a dilemma, for our problem is potentially unsolvable. Aspirin is safe and inexpensive; it probably reduces vein-graft occlusion; it may reduce complications involving the heart, brain, kidney, and intestine; and no other therapy is available. Given these circumstances, can a randomized clinical trial, wherein one group is deprived of aspirin, even be performed? If not, the clinician must adjudicate, for each patient, the cost–benefit ratio for early aspirin therapy.

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C-Reactive Protein in the Prediction of Cardiovascular Events

TO THE EDITOR: In the analysis by Ridker et al. (Nov. 14 issue),[1] several methodologic issues merit attention before claims of superiority for C-reactive protein in the prediction of cardiovascular risk can be substantiated. First, the authors did not adjust for body-mass index, which, given its strong correlation with C-reactive protein, is a major potential confounder of the relation between C-reactive protein and cardiovascular outcomes. Second, because high levels of low-density lipoprotein (LDL) cholesterol were undoubtedly treated during follow-up, the relation between LDL cholesterol and cardiovascular events was attenuated; similar treatment of high levels of C-reactive protein did not occur.

Third, in examining whether C-reactive protein adds to the Framingham risk score, the authors substantially hinder the predictive ability of the Framingham coronary-risk function[2] by using it to predict noncoronary as well as coronary events. Furthermore, in calculating Framingham risk scores, the authors used covariates (blood pressure, smoking, and diabetes) that were self-reported by the participants rather than measured systematically. Finally, the authors show that the addition of C-reactive protein to the Framingham risk score improves the prediction of modeled relative risk, rather than showing whether it improves the prediction of observed events. The model developed in this cohort must necessarily allow better prediction than the external Framingham model, particularly when the Framingham model is used to predict noncoronary events. It would be useful to know whether C-reactive protein adds to the Framingham risk score in predicting coronary events in a setting where its constituent risk factors are actually measured.

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1. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.
2. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.

TO THE EDITOR: Ridker et al. show that increased levels of C-reactive protein predict coronary events. The authors carefully adjusted their model for several known risk factors (such as age, smoking, and hypertension) but did not adjust for physical activity. There is mounting evidence that exercise, which reduces the risk of cardiovascular events, is also associated with decreased levels of C-reactive protein.[1-4] It would be important to know how much predictive power is left after adjustment for the level of physical activity. While we await more data, a good screening measure would be to ask patients about their level of physical activity.

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1. Mattusch F, Dufaux B, Heine O, Mertens I, Rost R. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. Int J Sports Med 2000;21:21-4.
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3. Ford ES. Does exercise reduce inflammation? Physical activity

and C-reactive protein among U.S. adults. Epidemiology 2002;13:561-8.
4. LaMonte MJ, Durstine JL, Yanowitz FG, et al. Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. Circulation 2002;106:403-6.

TO THE EDITOR: Ridker et al. suggest that the C-reactive protein level is a stronger predictor of first cardiovascular events than the LDL cholesterol level. They also suggest that the predictive value of C-reactive protein is enhanced when it is used with the Framingham risk score. These data support the possibility that C-reactive protein has a role in predicting cardiovascular events in this cohort. However, it is unwise to focus on the potential value of C-reactive protein as a biologic marker without considering the limitations of this and other homogeneous cohorts used to support the hypothesis.[1] The Women's Health Study is neither racially nor socioeconomically diverse. Although the study enrolled 39,876 professional women 45 and older, only 2.5 percent of the women in any treatment group were black.[2] The rate of death due to cardiovascular disease among black women 45 to 54 years old is 126.3 per 100,000, as compared with 41.2 per 100,000 among white women.[3] It is unclear whether the C-reactive protein level is more predictive of a first cardiovascular event than traditional cardiovascular risk factors on the basis of a study that excludes those at highest risk. Using the Framingham risk score with C-reactive protein may or may not augment the predictive value of C-reactive protein, because the Framingham risk score itself must be modified for use in blacks. Data from the National Health and Nutrition Examination Survey, a representative sample of Americans, suggest that C-reactive protein levels may be predictive among those with self-reported stroke, but the report concludes that further studies of C-reactive protein and cardiovascular disease in minority groups are needed.[4]

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1. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481-5.
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4. Ford ES, Giles WH. Serum C-reactive protein and self-reported stroke: findings from the Third National Health and Nutrition Examination Survey. Arterioscler Thromb Vasc Biol 2000;20:1052-6.

THE AUTHORS REPLY: Dr. Brezis correctly points out that physical activity is a critical component of any program aimed at the reduction of vascular risk and that available evidence suggests that exercise lowers C-reactive protein levels. According to our data, however, the effect of C-reactive protein on the risk of future vascular events is independent of activity level.

In contrast to the idea suggested by Drs. Lloyd-Jones and Levy, the use of lipid-lowering agents in the Women's Health Study was minimal during the first eight years of follow-up and therefore probably did not affect outcomes. Furthermore, as we have previously shown,[1,2] statins lower both LDL cholesterol and C-reactive protein levels. Therefore, even if statins were being used, these agents would have lowered the levels of C-reactive protein as well as those of LDL cholesterol and thus altered the predictive value of both variables.

We concur with Drs. Lloyd-Jones and Levy that the C-reactive protein level correlates with body-mass index. Indeed, the C-reactive protein level also correlates moderately with levels of high-density lipoprotein cholesterol, triglycerides, blood pressure, and plasma glucose, and abnormalities in all four of these variables are components of the metabolic syndrome. In this regard, we recently showed that C-reactive protein adds prognostic information to that achieved by the simultaneous use of all these interrelated risk factors.[3] Thus, C-reactive protein appears to add prognostic information at all levels of LDL cholesterol, at all levels of the Framingham risk score, and at all levels of the metabolic syndrome. Furthermore, as described in our article, analyses restricted to coronary events actually showed larger, not smaller, differences between the predictive value of C-reactive protein and that of LDL cholesterol. In those analyses, C-reactive protein values provided prognostic information at all levels of the Framingham 10-year risk (Fig. 1). We note, however, that there is nothing unusual about our finding that C-reactive protein is an independent predictor of noncoronary vascular events as well as coronary events. Indeed, the Framingham investigators themselves have published results showing

the value of C-reactive protein as an independent predictor of incident stroke,[4] and we have published similar data with regard to peripheral arterial disease.[5]

Last, we concur with Dr. Evans and colleagues that further study of C-reactive protein in minority populations needs to be done. In the Women's Health Study, the base-line levels of C-reactive protein are higher among black women and lower among Asian women than among white women — a pattern that parallels almost exactly the rates of vascular disease in these three groups.

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Editor's note: Dr. Ridker reports having been named as a coinventor on patents filed by Brigham and Women's Hospital that relate to the use of inflammatory biologic markers in cardiovascular disease.

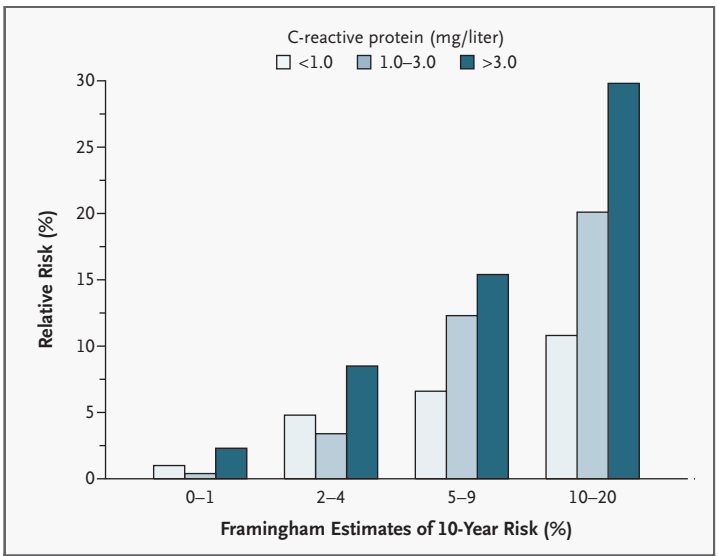

Figure 1. Relative Risk of Coronary Events at Various Levels of the Framingham Study Estimates of 10-Year Risk.

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3. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
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5. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481-5.

Reviparin after Leg Injury Requiring Immobilization

TO THE EDITOR: Lassen et al. (Sept. 5 issue)[1] note the high risk of venous thrombosis in patients with leg injury requiring immobilization, as well as previous studies of prophylaxis in this population. Given this high risk, none of the participants in their study should have been treated with placebo.

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1. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med 2002;347:726-30.

TO THE EDITOR: Lassen et al. did not address the possible influence of surgery on the incidence of thromboembolic events in their study. The surgical procedure itself and related factors, including the site, technique, and duration of the procedure, the type of anesthetic, and the presence of infection, may affect the risk of venous thrombosis.[1] Could the authors provide data on the incidence of venous thromboembolism in patients who underwent surgical treatment and in those who did not?

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Editor's note: Dr. Girard reports having received honorariums for consulting and speaking from Aventis Pharma, Leo Pharma, and AstraZeneca.

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001;119:Suppl:132S-175S.

TO THE EDITOR: Lassen et al. did not provide information on the race or ethnic group of the patients enrolled in their study. The indication for thromboprophylaxis may need to be tailored according to race or ethnic group.