We were aware of both these papers during our study, but we failed to refer to them as they represent different patient populations to our own. However, we agree that, as we did not present data on the diurnal variation in soluble P-selectin and soluble thrombomodulin in healthy subjects, we were perhaps premature to interpret this data in terms of "loss" of a pattern in the patients with AF, although this lack of diurnal variation is in keeping with our hypothesis of a "constant" hypercoagulable state in AF.

Naturally, there are many confounders to be addressed in studies of thrombosis and hemostasis, and ours is typical in that atherosclerosis and its risk factors were present in some of our patients with AF. It has previously been shown that the hypercoagulable state in AF is independent of underlying etiology or associated heart disease (9), and we would emphasize that the main objective of our study was to assess the circadian or diurnal variation in the hypercoagulable state in AF, rather than to reproduce many previous analyses (including our own) of the effects of heart disease on hypercoagulability in AF. Indeed, we were unable to find any difference in our research indices comparing those patients with lone AF with those whose AF was confounded by other disease (1). Despite this, our cohort of patients are indeed characteristic of those presenting to the hospital with AF, and so the data are truly representative of a "real-life" situation.

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C-Reactive Protein and Electron Beam Computed Tomography: A Perfect Match?

Redberg et al. (1) are incorrect in concluding that electron beam computed tomography (EBCT) may not predict future coronary events because there is no evidence of a positive association between C-reactive protein and coronary calcium. The presence of atherosclerosis (EBCT calcium) and inflammation (C-reactive protein) are both predictors of future events. This study adequately demonstrated that the two are not dependent upon one another. Published data from the Cholesterol And Recurrent Events (CARE) trial demonstrated that many patients with established coronary disease (myocardial infarction [MI]) had normal or low C-reactive protein levels (2). The significant finding in the CARE study is that coronary disease plus inflammation (C-reactive protein) predicted future events. However, it is incorrect to assume that a low C-reactive protein in the setting of MI is protective. These patients are still at greatly increased risk over non-MI persons. Lack of association of C-reactive protein with EBCT does not imply that EBCT, nor C-reactive protein, will fail to predict cardiac events.

The investigators made a series of small errors with the EBCT literature that deserve comment. They quote a fluoroscopy study stating that individuals with normal EBCT scores may nonetheless suffer MI. EBCT is significantly more sensitive than fluoroscopy for detection of coronary disease and prediction of future cardiac events. They also state that calcium score is a weak predictor of coronary death and infarction. A recent meta-analysis of EBCT demonstrated there was an increased risk for hard events: MI or death (summary risk ratio 4.2 using median calcium scores) (3). When studies evaluate the highest quartile of calcium score as compared with the lowest quartile, odds ratios (ORs) are on the order of 10 to 20 (4–6). Thus, EBCT is potentially as robust a predictor of future cardiac events as C-reactive protein (OR of 4.4 using quartile analysis) (7).

The question answered in the paper is that not every asymptomatic person with atherosclerosis has inflammation, which was known from the CARE study. Atherosclerosis predicts future cardiac events, inflammation predicts future events, and the combination more strongly predicts future events (2). The detection of atherosclerosis (calcium by EBCT) and inflammation (C-reactive protein) might predict future events robustly, and this is actively being investigated.

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REPLY

We appreciate Dr. Budoff’s interest in our paper on C-reactive protein and calcium in postmenopausal women. The hypothesis tested in our study (1) was whether postmenopausal women enrolled in the Females, Lipids, Activity and Sex Hormones (FLASH) study with coronary calcium by electron beam computed tomography (EBCT) would have higher concentrations of high sensitivity testing for C-reactive protein (hsCRP), an inflammatory marker believed to be an independent risk factor for cardiovascular disease (2). However, we found no evidence of a positive association of hsCRP and calcium by EBCT. We suggested that hsCRP may be a marker for inflammation and EBCT may be a marker for mature and more stable atherosclerotic plaque. We also stated that these data highlight the importance of careful prospective clinical evaluation of emerging technologies such as EBCT, the same conclusion reached by the recent American College of Cardiology/American Heart Association (ACC/AHA) Expert Consensus panel on EBCT (3).

Dr. Budoff takes issue with our statement that “individuals with normal EBCT scores may nonetheless suffer MI.” However, this statement is supported by the data not only in the paper referenced, but also in papers by Secci (4) (ref. 27 in the paper), Arad (5) (ref. 14 in the paper), South Bay Heart Watch (6) (ref. 28 in the paper), Raggi (7), and by the recent ACC/AHA statement (3).

In addition, Dr. Budoff states that the “question answered in the paper is that not every asymptomatic person with atherosclerosis has inflammation, which was known from the CARE study.” However, as the CARE study exclusively studied patients after myocardial infarction, it did not provide any information about asymptomatic persons. Similarly, the FLASH study patients were all asymptomatic, but many did not have atherosclerosis.

interpretation of these papers is inconsistent with their study designs.

Finally, the CARE study did not measure EBCT scores. Hence, Dr. Budoff’s statement that the CARE study (8) showed that the “combination [calcium scores and hsCRP levels] more strongly predicts future events” is incorrect. However, we agree with Dr. Budoff that this is an important hypothesis to test.

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