of revascularization were the only predictors of the extent of plaque burden, whereas the established cardiovascular risk factor low-density lipoprotein cholesterol (LDL-C) showed no statistically significant relation to the amount of plaque burden (1).

Our group serially assessed left main stems of patients with coronary artery disease treated by usual care with IVUS. Similar to the findings of Nicholls et al. (1), at baseline (single-point observation) we also found that patients with low versus high LDL-C levels had no difference in coronary plaque burden (2). However, our patients with high LDL-C levels showed significantly more plaque progression during IVUS follow-up (serial observation) (2). Using these data, we were able to show for the first time a significant linear relation between LDL-C levels and coronary plaque progression as directly measured by IVUS (2); later, this was confirmed by large pharmacological intervention trials with serial IVUS (3).

The aforementioned pieces of evidence suggest that the extent of atherosclerotic plaque burden, as assessed at a single point in time, does not sufficiently predict the rate of plaque progression during follow-up. The extent of plaque burden can be in a balance between plaque progression and regression. In other words, plaques may be “progressors” despite a relatively small plaque burden, and plaques may be “regressors” despite a relatively great plaque burden. This underlies the fact that single-point observations are unable to characterize the “dynamic status” of coronary lesions.

Coronary remodeling (changes in total vessel size) may be partly responsible for the contradiction between the findings of single-point versus serial assessment when analyzing percent plaque burden. Plaque burden is in fact the relation between total vessel and plaque size; if plaque size remains unchanged but vessel size decreases (“negative remodeling”), the calculated percent plaque burden increases; and if total vessel size increases (“positive remodeling”), plaque burden decreases. Although the remodeling index shows a relatively close relationship with the subsequent direction of true serial remodeling (4), we were unable to demonstrate a relation between plaque burden and changes in total vessel dimensions (i.e., serial remodeling) (5), which underlies the relative independence of actual coronary remodeling from baseline plaque burden.

Finally, serial observational ultrasound data suggest that coronary plaque progression by IVUS may be associated with increased cardiovascular risk (6). We found that patients at the highest estimated cardiovascular risk, as derived from 3 established cardiovascular risk scores, showed the highest plaque progression rates; in addition, patients with greater plaque progression had significantly more actual cardiovascular events during follow-up (6).

Thus, we believe that serial assessment of coronary plaques (progression–regression)—if possible with volumetric analyses (7)—should be the “gold standard” when analyzing the relation between cardiovascular risk factors and coronary atherosclerosis.

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REPLY

We read with interest the letter by Drs. von Birgelen and Hartmann with regard to our use of serial versus static assessments of atheroma burden using intravascular ultrasound (IVUS) (1). Although static assessments do not adequately evaluate the dynamic process of arterial wall remodeling, the ability to apply a cross-sectional appraisal of a cohort of subjects provides a unique opportunity to investigate factors that correlate with the extent of atheroma throughout a coronary arterial segment. Serial assessments of atheroma burden have assumed a pivotal role in the elucidation of the factors, including pharmacological interventions, that influence the natural history of atherosclerosis. It is for this reason that the serial assessment of atheroma burden by IVUS has become a surrogate end point in clinical trials (2–7).

The previous studies of the left main coronary artery cited by these investigators (8) raise a number of important points with regard to the study of atherosclerosis. A major limitation of these studies includes their measurement of atheroma area at a single cross-sectional slice of the left main coronary artery in a small number of subjects (n = 60), which were deemed to have the smallest lumen area at baseline. As a result, these researchers used the single image that corresponded to the most severe angiographic stenosis in one specific segment of the coronary anatomy to make speculative assessments of atherosclerosis. Given that atherosclerosis is a systemic and not a focal process that would fit in a single ultrasound frame, in addition to the well-established discord between angiographic abnormalities and the extent of atheroma within the arterial wall, it is uncertain what conclusions can be made from investigating disease at one site.

The problem of using a single slice is further magnified in serial studies. Serial assessment of atheroma burden requires precise matching of that single slice, a task that is difficult to achieve in many cases. In contrast, our report describes the relationship between a broad range of clinical parameters and the volume of
atheroma throughout a segment of coronary artery of at least 30 mm in length (1). This was performed in a large cohort of subjects and includes sites that do not contain significant obstructive disease. Although one segment was studied in each subject, each epicardial coronary artery is reflected in the total cohort (i.e., this is not a study of disease limited to the left main segment). Further, the volumetric approach defines segments by the fixed anatomic presence of arterial side branches and provides a greater opportunity for precise matching and investigation of the factors that influence the natural history of atherosclerosis.

Studying atherosclerosis within the left main coronary artery, the investigators found no significant correlation between the level of low density lipoprotein (LDL) cholesterol and atheroma burden (8), in support of our findings. Interestingly, they found a significant correlation between baseline LDL cholesterol and progression of atheroma at the region studied. The degree of correlation was much greater than what has been subsequently been reported for the relationship between the degree of change in LDL cholesterol and atheroma volume in patients treated with a statin (6). Given that atherosclerosis is a complex pathological process that results from the influence of a large number of factors on the arterial wall and that there is a substantial overlap between levels of LDL cholesterol and incidence of cardiovascular disease, it would be surprising to expect anything greater than a mild correlation between these factors at most.

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Most Asymptomatic Diabetic Patients Will Not Benefit From Coronary Revascularization

In a study recently published in JACC, Scognamiglio et al. (1) suggest that patients with type 2 diabetes mellitus with ≤1 other risk factor should undergo routine stress imaging to diagnose asymptomatic coronary artery disease (CAD), a strategy the investigators believe will lead to early aggressive medical treatment and more favorable coronary anatomy that is more suitable for revascularization.

As cited by Scognamiglio et al. (1), the risk of major coronary events in diabetic patients is similar to that of nondiabetic patients with established coronary disease. Risk factors in these patients should be treated as aggressively as in CAD patients even without evidence of CAD on diagnostic imaging. Therefore, routine assessment of asymptomatic diabetic patients by stress imaging to clarify the need for more aggressive risk-factor modification is not warranted.

Both coronary revascularization by surgery (coronary artery bypass graft [CABG]) and percutaneous coronary intervention (PCI) differ in their influence on prognosis. Although no randomized study to date has shown PCI to improve elective patient prognosis, CABG improves survival of elective patients in 4 categories: patients with left main coronary disease; patients with 3-vessel disease and decreased left ventricular function; patients with multivessel disease involving the proximal left anterior descending artery; and patients with diabetes mellitus and multivessel disease (2). Most other patients undergo revascularization for control of symptoms. For asymptomatic patients to benefit prognostically from revascularization, one of the 4 previously mentioned indications must apply (and the procedure should be CABG), otherwise no mortality benefit should be anticipated. Revascularization, therefore, should be limited to patients who are symptomatic or fall under 1 of the 4 previously mentioned categories. Noninvasive testing should be performed in asymptomatic diabetics only if clinical assessment suggests that they belong to a high-risk group. Only those patients with impaired cardiac function or high-risk stress imaging should undergo coronary angiography.

Early detection and aggressive modification of non–insulin-dependent diabetes mellitus and other risk factors in adherence to published guidelines (3,4) will help prevent CAD and its complications, whereas routine stress imaging and revascularization for the most part will not.

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