artery disease (CAD), an area of research in need of long term follow up studies like this one (mean follow-up >4 years).

However, we noticed that the mean pre-test probability of CAD in the study population was 42.5%, with one-quarter of the patients having a high CAD probability, which is not in line with the most favored low-to-intermediate probability population referred for CTA for the exclusion of possible CAD (2), and that could explain the higher-than-expected hard event rate for a stable CAD population (almost 1 out of 2 patients with obstructive CAD dying or having a nonfatal myocardial infarction [MI]) in the follow-up (3). This could have been the result of having included patients admitted to the hospital because of new-onset chest pain (43%), a subset that could be considered as possible acute coronary syndrome (ACS) unstable angina/non–ST-segment elevation MI) and can explain the higher than expected rate of major (death/MI) events in the follow-up (event-free survival of 54%). In how many cases was an ACS diagnosis confirmed? If any, the authors should have excluded these patients from the study. We fully agree that CTA can provide useful prognostic information beyond the exclusion of obstructive CAD, but the inclusion of patients with possible ACS and high CAD probability could have lead to an overestimation of the prognostic power of CTA.

Another striking point was the fact that 45% of patients had hypercholesterolemia but only 26% were treated with statins. Further, statins turned out in multivariable analysis to be independent predictors for hard events. Likewise, 26% of the population (with suspected CAD) was taking aspirin, which is not generally recommended as primary prevention. Use of aspirin was also an independent predictor of all cardiac events. It would have been interesting to know if the use of these drug groups is allocated to a more severe subset of patients (more frequently used in obstructive vs. nonobstructive vs. normal patients) and in this way are just a surrogate marker of higher disease burden. Likewise, it would be of interest to know if patients were already taking these drugs before the CTA or if they were just started after significant disease was identified and, in this way, they could not have had enough time to come out with its protective effects in a more severe CAD subgroup of patients.

The Framingham risk score (FRS) was used to estimate the cardiovascular risk of this Italian cohort of patients; it could have been more accurately estimated with the European-based HeartScore (4). This could have also influenced the results, as the multivariable analysis models were adjusted for the FRS.

It is not mentioned that the events were independently adjudicated and that the adjudication event committee is an experienced one with acceptable intra-committee reproducibility for the adjudication of events. This point is of utmost relevance in a report of this nature. In addition, regarding *revascularizations*, we agree that early revascularizations should be excluded to avoid the influence of CTA results in patient management but most of the previous studies considered early as 30 days (5) and not 6 months like in the paper from Andreini et al. (1). This could have also influenced the results, as revascularizations in obstructive CAD group are likely to have happened sooner after the CTA and in this regard could have underestimated the prognostic value of obstructive versus nonobstructive CAD. Further, it is not mentioned whether the revascularizations were ischemia-driven (i.e., only for obstructive lesions) or not.

Despite the fact that authors have scored hierarchically the plaque type per segment (i.e., in case of presence of 2 plaques, calcified and noncalcified, only one was scored and labeled as calcified) which underestimates the frequency of noncalcified plaques, in the univariate analysis, these were found to be independent predictors of hard events. This methodology seems to us to be counterintuitive, since it has been reported many times that high-risk plaques (i.e., plaques prone to rupture and associated with an event) are those noncalcified or mixed, which could have come out as strong predictors also in the multivariate analysis if the authors had not underscored them.

Undoubtedly, this is a report with an important message, but we feel that the above-mentioned points should be further explained to strengthen the conclusions.

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REPLY

The comments of Garcia-Garcia and Goncalves are relevant and allow us to expand on some results of our study (1). First, we found

a relatively high cumulative event rate at follow-up in multidetector computed tomography coronary angiographic (MDCT-CA) obstructive coronary artery disease compared with other studies, which may be due to characteristics of patients who had chest pain and positive stress tests in 43% and 29% of cases, respectively. However, the CONFIRM registry demonstrated that MDCT-CA has the best prognostic value in this patient subset, whereas its value in asymptomatic patients is quite limited (2). We agree that including patients with acute coronary syndromes (ACS) may lead to an overestimation of MDCT-CA prognostic capability. Accordingly, we excluded patients in whom ACS was confirmed by cardiac enzyme or electrocardiographic changes. The discrepancy between hypercholesterolemia rate and statin use in our patients is in agreement with the suboptimal therapy adherence reported in a substantial proportion of European patients (3). Medical therapy reported in our patients was administered before MDCT-CA. Indeed, 26% of them were taking aspirin, not for CAD but for other indications. We agree that the European Heart Score would have been more appropriate than Framingham cardiovascular risk estimation. However, the former has been challenged because it is not mathematically consistent and unfit to estimate cardiovascular mortality (4). In the first version of our paper, revascularizations were defined "early" if performed within 2 months after MDCT-CA. However, a reviewer criticized this definition. Indeed, using a 2-month cutoff, only 6 patients were excluded despite 295 patients having MDCT-CA stenosis ≥70%. This indicates that many revascularizations occurring later than 60 days were probably driven by MDCT-CA. We agree that the 6-month cutoff may have led to an underestimation of obstructive CAD prognostic value. However, this limitation did not affect hard cardiac events survival analysis. Finally, we believe that assigning 1 coronary plaque per coronary segment and classifying a plaque as calcific in cases in which a coronary segment contained calcific and noncalcific plaques was correct, as previously reported (5). Indeed, in the presence of small plaques, those calcific plaques are the easiest to detect with MDCT-CA, and most prognostic data are based on simple coronary plaque scores, regardless of plaque composition (3).

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Ultrasonographic Measure of Carotid Plaque Burden

In their excellent paper, Sillesen et al. (1) omitted mention of the original work on measurement of carotid plaque burden. Spence et al. (2) first measured carotid total plaque area (TPA) in 1990, and developed it for patient management and genetic research, and 3-dimensional methods for evaluation of new therapies. They showed that TPA and progression of TPA strongly predicted the 5-year risk of stroke, death, or myocardial infarction after adjusting for coronary risk factors.

Sillesen et al. (1) stated that the prevalence of plaque they observed (78%) was 2-fold higher than previously reported. However, in the NOMAS (Northern Manhattan Study) study, a population-based study of individuals free of stroke at similar ages, plaque prevalence was 58% on 2-dimensional ultrasound imaging and it was greater by age and among certain race-ethnic groups (3). Prevalence of plaque depends on age and how it is defined. If defined as a focal thickening >1 mm, in vascular patients it increases from 75% of patients at age 35 to 45 years to 99% by age 65 to 75 years, and 100% over age 75 years (2).

Besides plaque burden, other ultrasonographic characteristics of plaque morphology such as plaque surface irregularity, ulceration, texture, and plaque density may be even more important predictors of stroke and cardiovascular disease.

The Tromsø study showed that TPA was a stronger predictor of myocardial infarction and stroke (4) than intima-media thickness, and this was confirmed in a meta-analysis (5). Three-dimensional plaque volume is highly correlated with TPA, and is much more sensitive to change with therapy than intima-media thickness or TPA, so it is the best way to assess effects of new therapies (2). There is little doubt that carotid plaque burden will be a stronger predictor of cardiovascular events in the High Risk Plaque Bioimaging Study than any of the other imaging modalities measured, with the possible exception of coronary calcium.

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Please note: Dr. Spence holds an interest in Vascularis.com.

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