attention to the interpretation of intravascular images and know the limitation of the diagnostic accuracy of optical coherence tomography (OCT) for thrombus formation within the coronary artery tree. A combination of imaging devices and close observation of the surrounding vessel wall could help the interpretation of these images.

Although it is widely accepted that a CN has the potential to develop a coronary thrombosis (2,3), the pathogenesis and microstructure of a CN are still a mystery. In our experience, a protruding calcified lesion of a coronary artery, which could be defined as a classic calcified nodule, always shows a fibrin-rich calcium-containing nodule. The superficial platelike calcification within the intima generally contains minimal fibrin deposition. The distinct histological features of a CN compared with nonnodular calcification suggests the differential etiology for these 2 types of calcification.

Examination of ex vivo imaging and histology by our serial autopsy cases identified tiny calcified nodules, which are exactly like the images in your previous presentation (4). These small CNs could interpret red luminal thrombus by OCT. We should be mindful that an irregular protruding bright mass with shadowing could represent a CN on OCT. Continuous effort to compare coronary imaging and histopathology of multifarious atherosclerotic lesions in human coronary arteries is recommended by both the pathologist and cardiologist.

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The Optimal Cutoff Value for Left Main Minimal Lumen Area of 4.5 mm^2: A Word of Caution

We read with interest the elegant work by Park et al. (1) assessing the optimal left main (LM) minimal lumen area (MLA) criteria to identify hemodynamically significant stenoses. Due to the potential major clinical implications of these findings, some relevant issues should be addressed. First, the LM-MLA cutoff value seems to be population dependent. A previous U.S. study yielded a cutoff value of 5.9 mm^2 (sensitivity, 93%; specificity, 94%) for a fractional flow reserve (FFR) <0.75 (2). The average LM-MLA in the patients included in these 2 studies was strikingly different (7.6 mm^2 in the U.S. study and 4.8 mm^2 in the Korean study). The most plausible explanation for such differences appears to be ethnicity related. Another recent study compared coronary LM lesions between 99 white North American and 99 Asian patients (3). Again, Asian patients had a significantly smaller LM-MLA (5.2 ± 1.8 mm^2 vs. 6.2 ± 1.4 mm^2; p < 0.0001). Accordingly, we believe that the attempts by Park et al. (1) to adjust for body mass index in their series of 112 Asian-only patients cannot exclude this important influence. Second, given the unique prognostic implications of LM-derived ischemia, the optimal cutoff value must show very high sensitivity and negative predictive values. This is the case for a cutoff value of 6 mm^2 (1,2). In a previous study (4), we found that in patients with an LM-MLA ≥ 6 mm^2, revascularization could be safely deferred. Moreover, we suggested that in patients with LM-MLAs of 5 to 6 mm^2, clinical decisions should be individualized or, even better, informed with the FFR if feasible. In the current study (1), the sensitivity (77%) and negative predictive value (75%) for a 4.5-mm^2 cutoff value were clearly suboptimal. Notably, among the 54 lesions with an LM-MLA >4.5 mm^2, 13 (24.1%) had an FFR of ≤ 0.80. We honestly believe that missing 1 in 4 patients with severe ischemia is not justified in this challenging scenario. Third, a theoretical LM-MLA cutoff value may be nicely derived from fractal geometry. A study confirmed that the linear law was more exact in this regard than Murray's law, which largely underestimated the calculated mother vessel diameter (5). Using the currently established 3 mm^2 as the best cutoff value of MLA for the LM branches (6), the calculated LM-MLA cutoff value by linear law is 5.8 mm^2. Fourth, the optimal

LM-MLA cutoff value should be prospectively validated. In the LITRO (4), a prospective multicenter study including 354 patients, the 6-mm² cutoff value was clinically validated. At 2 years, the outcome of deferred patients was equivalent to that of the revascularized group. Importantly, the outcome of the few patients with 5- to 6-mm² LM-MLA who did not undergo revascularization was significantly worse. Last but not least, the LM-MLA cutoff value is just aimed to exclude the presence of current ischemia. However, 36% of patients in the study by Park et al. (1) with "isolated" LM disease presented as an acute coronary syndrome, and on intravascular ultrasound, plaque ruptures (30.6%) and intracoronary thrombi (33.3%) were readily observed. It is difficult to believe that the fate of these unstable plaques may be only dictated by the hemodynamic significance encountered at the time of the examination.

We strongly believe that the provocative proposal of 4.5 mm² as an LM-MLA optimal cutoff value should be taken very cautiously until further clinical data support its prognostic validity.

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REPLY: The Optimal Cutoff Value for Left Main Minimal Lumen Area of 4.5 mm²: A Word of Caution

We thank Dr. de la Torre Hernández and colleagues for their interest in our paper (1) suggesting the optimal left main coronary artery minimal lumen area (LM-MLA) of 4.5 mm² for detecting fractional flow reserve (FFR) <0.80.

First, the Jasti et al. (2) study with a small sample size (N = 55) reporting an LM-MLA cutoff value of 5.9 mm² enrolled patients with lesions with downstream disease of the LM branches; 58% were distal LM lesions usually extending to the side-branch ostia, which made assessing how the LM-MLA itself affects the hemodynamic significance unreliable. Moreover, they included only a few patients with an MLA of 4.5 to 6.0 mm². The lesions mostly had a large lumen, with 75% having a negative FFR. Conversely, our study (N = 112) included only ostial and shaft lesions: 34 patients with an LM-MLA of 4.5 to 6.0 mm² and more ischemia-inducing lesions and 59% with positive FFR (<0.80). That is the main difference in our study. The ethnic differences poorly supported the relevance of using the larger LM-MLA criterion. Rusinova et al. (3) reported a smaller LM-MLA in Asian patients, whereas the vessel area was greater in Asian compared with North American patients (20.7 ± 4.5 mm² vs. 19.3 ± 4.2 mm², p = 0.024).

Second, the suboptimal accuracy of the LM-MLA is not surprising. Even in isolated LM lesions, the FFR was determined not only by the LM-MLA but also by various clinical and lesion-specific local factors (age, body mass index, left ventricular mass, and the presence of plaque rupture) (1). In patients with an LM-MLA >4.5 mm², the FFR was <0.80 in 24%, but <0.75 in only 9%. However, 36% of the patients with an LM-MLA <6.0 mm² showed an FFR >0.80, and they are at risk of undergoing unnecessary treatment.

Third, if an MLA of 3.0 mm² for the left anterior descending artery and 2.7 mm² for the left circumflex artery are assumed to be ischemic thresholds, clearly the LM-MLA is 4.5 mm² (Murray's law) (1).

Fourth, in the LITRO trial (4), 16 of the 168 patients with an LM MLA <6 mm² did not undergo revascularization. They had an LM-MLA of 5.0 to 6.0 mm² and had complex lesion morphology for PCI, high surgical risk, old age, and multiple comorbidities. The worse