

EDITORIAL

Imaging and Physiology Get Along in the Left Main Coronary Artery Disease

The Case for Intravascular Ultrasound and Instantaneous Wave-Free Ratio

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ANGIOGRAPHICALLY ELUSIVE LEFT MAIN CORONARY ARTERY: INTRAVASCULAR ULTRASOUND AND FRACTIONAL FLOW RESERVE TO THE RESCUE

The left main coronary artery (LMCA) is the segment that shows the most difficulties for an adequate angiographic evaluation. Furthermore, when the stenosis is intermediate (40%–70%), its categorization as significant or not is practically unfeasible. For this reason, the use of pressure wire and intravascular ultrasound (IVUS) has been studied and validated in this particular setting.^{1,2} A pooled analysis demonstrated that deferring LMCA intermediate stenosis on the basis of fractional flow reserve (FFR; cutoff, 0.8) or minimum lumen area (MLA; cutoff, 6 mm²) showed an acceptable and similar risk of events in a midterm follow-up.³

See Article by El Hajj et al

This is so because in LMCA, unlike other coronary segments, there is a better correlation between FFR and MLA. However, correlation studies between both metrics have yielded different values for MLA (4.5 and 6 mm²).^{4,5} This is explained by the different populations of the respective studies, Asian and Westerners. However, for the practical use of an LMCA MLA cutoff value, given the unique prognostic implications of LMCA-derived ischemia, the optimal value must show a very high sensitivity and negative predictive values, which is true for 6 mm² but not for 4.5 mm², and should be prospectively

validated as the 6 mm² cutoff was in the LITRO study (Estudio de Lesiones Intermedias del Tronco Comun).^{2,6} Therefore, the value of 6 mm² more than a predictive cutoff of ischemia derived from a correlation with FFR should be interpreted as a cutoff for a safe deferral of revascularization (Figure).

NEWCOMER IN LMCA ASSESSMENT: THE INSTANTANEOUS WAVE-FREE RATIO

The advantages of instantaneous wave-free ratio (iFR) in the LMCA are obvious, avoiding the use of adenosine and showing less interaction with the presence of downstream lesions in left anterior descending artery (LAD) or left circumflex artery (LCx). However, in the trials comparing iFR versus FFR, LMCA lesions were excluded or minimally represented. This led to the conduct of studies that sought to examine the correlation between iFR and FFR in LMCA disease, which showed an excellent classification agreement, with most disagreement (19%) occurring within a narrow FFR range falling within the so-called gray zone.⁷

In agreement with these results, the DEFINE LM registry (Revascularization Deferral in Patients With Left Main Coronary Artery Disease Based on iFR Evaluation) has evaluated the use of iFR (cutoff, <0.9) to indicate revascularization in 314 patients with intermediate LMCA lesions, showing good results comparable to those observed with FFR.⁸

In this issue of *Circulation: Cardiovascular Interventions*, El Hajj et al⁹ present the results of a multicenter retrospective registry including 125 patients who underwent

Key Words Editorials ■ constriction, pathologic ■ coronary vessels ■ follow-up studies ■ hemodynamics

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

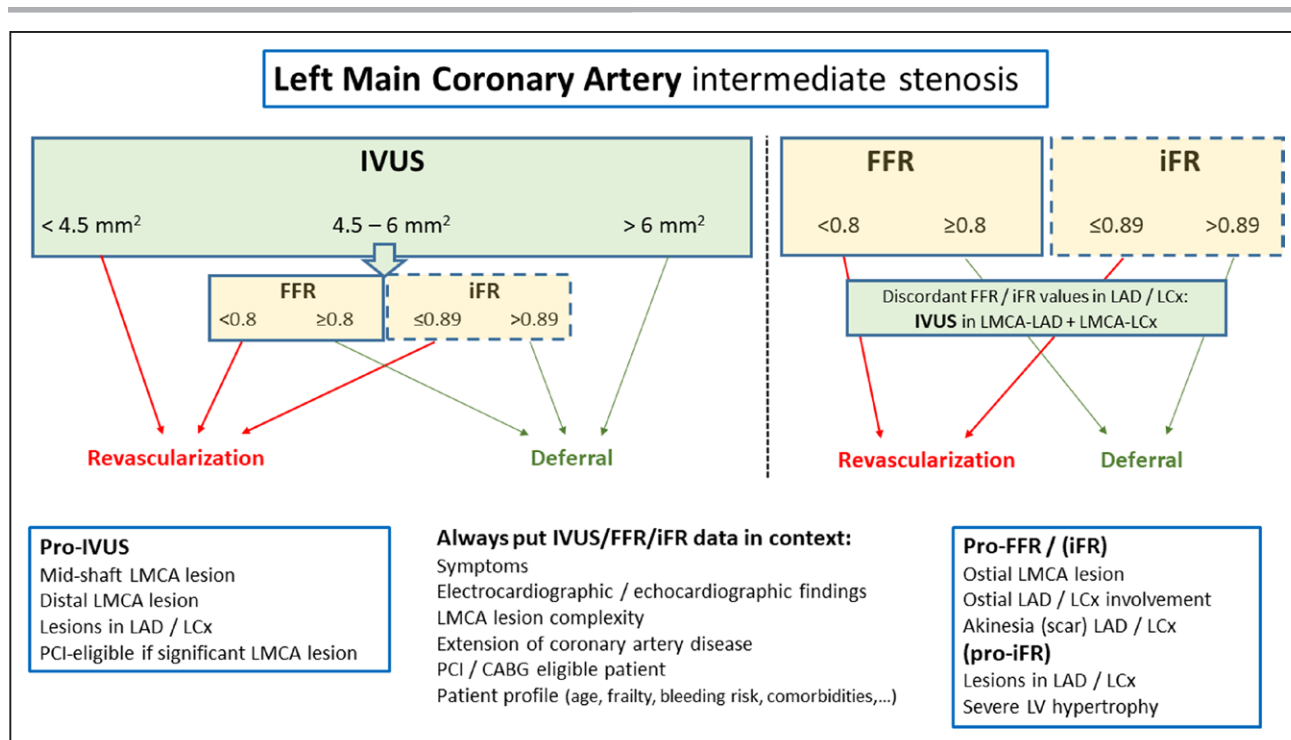


Figure. Alternatives and integrated approach to the assessment of the intermediate left main coronary artery (LMCA) disease. Intravascular ultrasound (IVUS) and fractional flow reserve (FFR) are well established, whereas instantaneous wave-free ratio (iFR) could require more additional data. CABG indicates coronary artery bypass grafting; LAD, left anterior descending artery; LCx, left circumflex artery; LV, left ventricle; and PCI, percutaneous coronary intervention.

both iFR and IVUS evaluation for intermediate LMCA stenosis. Using an MLA of 6 mm² as the cutoff, iFR showed 77% sensitivity, 66% specificity, and 0.77 area under the curve. Among the 69 patients without ostial LAD or LCx disease, values were 70%, 84%, and 0.84, respectively. The correlation was not significantly different when the body surface area was considered.

The study is truly pertinent, well conducted, and adds support to the use of iFR in LMCA assessment.

Nonetheless, the concurrence of both techniques in a retrospective study may imply some selection bias, suggesting the inclusion of (1) cases showing an MLA in the range of more uncertainty (4–7 mm²), which motivated the use of the pressure wire or (2) cases with IVUS performed because the FFR/iFR values resulted borderline. In both circumstances, this selection bias could affect the correlation with respect to a more open and less biased inclusion. In fact, the median LMCA MLA was notably smaller compared with the LITRO registry, 4.9 (3.7–6.9) versus 6.7 (5.2–9.5), respectively.^{2,9}

In this registry, patients with downstream stenosis in LAD and LCx were included. In these cases, the iFR was measured between the LMCA and those lesions, assuming the higher reliability of the iFR in the presence of tandem lesions as compared with FFR. This assumption could be fairly right provided the stenosis in LAD and LCx is not >90%. However, iFR values in between lesions (apparent LMCA iFR) could be slightly higher than the value obtained after treating the distal lesion

(true LMCA iFR), and this may be relevant when the in-between lesion iFR is borderline negative.

The most common location of LMCA disease is the distal, involving to a different extent the ostium of LAD and LCx. In this study, when both vessels were evaluated, the highest value was taken considering that the lowest would reflect the additional ostial contribution in the corresponding vessel. This is reasonable but somehow questionable. In general, the LAD has more resting flow than the LCx, and for a given MLA of the LMCA, the iFR may be lower in LAD. These differences are much greater with FFR, but they could be not negligible with iFR in some cases.

The MLA cutoff for the LMCA could be influenced by body size, and the sensitivity analysis with body surface area could have accounted for the sexual and racial effects. Moreover, the correlation of iFR to an indexed IVUS MLA/BSA showed similar results. However, the investigators could not account for all the possible confounders such as myocardial mass because of the small sample size or lack of data.

The study included parallel assessment with FFR in 75 (60%) patients, detecting discordance in 21% around the cutoff, similarly to the previously reported.⁷ The full availability of FFR would have added more value to this analysis.

As the last issue to be highlighted is the lack of clinical follow-up in deferred cases.

In sum, the present study provides additional information in favor of considering iFR in the assessment of LMCA

lesions; however, as the authors themselves acknowledge, we should be cautious on how we implement the findings of the current study in the clinical practice.

INTEGRATED APPROACH IN LMCA DISEASE: IVUS AND PHYSIOLOGY

To evaluate intermediate lesions of the LMCA, what is best, IVUS or pressure wire? and if we use the latter, by FFR or iFR? There is no right/wrong answer to these questions. IVUS and pressure wire have their advantages and shortcomings, but both techniques have proven to be safe and effective to discriminate and help in the clinical decision. Regarding whether FFR or iFR, although there are already several studies that point to the validity of the nonhyperemic index in this indication, some more evidence is still needed.

However, whatever first-line technique we use, it will not be so uncommon to have to resort to the other technique for a more accurate assessment of the LMCA disease. This was what happened in the cases included in the herein discussed study, and this integrative approach is what I advocate (Figure).

Future studies are needed to investigate how we can integrate iFR with IVUS findings in this challenging scenario. In this sense, our group is currently conducting the iLITRO study (Concordance Between FFR and iFR for the Evaluation of Intermediate Lesions in the LMCA. A Prospective Validation of a Predetermined Value for iFR; <https://www.clinicaltrials.gov>; unique identifier; NCT03767621) which will include 300 patients with intermediate lesions of the LMCA in whom the assessment is performed with iFR and FFR as well as with IVUS in cases with discordant information between both pressure indices.

There are no excuses for not implementing precision medicine in the management of LMCA disease.

ARTICLE INFORMATION

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Disclosures

Dr de la Torre Hernandez claims receipt of grants and research support from Abbott Medical, Biosensors, Bristol Myers Squibb, and Amgen. Also, he claims receipt of honoraria/consultation fees from Boston Scientific, Philips-Volcano, Medtronic, Biotronik, AstraZeneca, and Daiichi Sankyo.

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