# Revascularization of non-culprit lesions: A common dilemma

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In recent years, there has been a considerable interest concerning diagnostic and therapeutic strategies in patients with coronary artery disease (CAD).[1,2] Primary percutaneous coronary intervention (PCI) is the preferred method of re-perfusion for patients with ST-segment elevation myocardial infarction (STEMI).[3,4] Restoring normal coronary blood flow and normal myocardial perfusion are primary goals for the interventional cardiologist performing the procedure. The 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for coronary artery revascularization stated that staged percutaneous intervention of a significantly stenosed culprit artery in patients presenting with STEMI is recommended in select patients to improve outcomes.[5] Percutaneous intervention of the non-culprit artery at the time of primary PCI is less clear and may be considered in stable patients with uncomplicated revascularization of the culprit artery, low-complexity non-culprit artery disease, and normal renal function. In contrast, percutaneous intervention of the non-culprit artery can be harmful in patients in cardiogenic shock.[5] Approximately 40% to 70% of STEMI patients undergoing primary PCI have multivessel CAD.[6] PCI options for patients with STEMI and multivessel disease include primary PCI of the culprit arteries, with PCI of non-culprit arteries only for spontaneous ischemia or intermediate or high-risk findings on pre-discharge noninvasive testing and primary PCI of culprit arteries followed by staged routine PCI of non-culprit vessels. Non-culprit lesions, which are usually discovered incidentally at the time of primary PCI, may represent stable coronary artery plaques, for which additional revascularization may not offer additional benefit.[7] However, if non-culprit lesions have morphologic features consistent with unstable plaques, which confer an increased risk of future cardiovascular events, there may be a benefit of routine non-culprit-lesion PCI. The decision on which approach to use has been a subject of debate and what is the best choice to determine physiologically significant lesions of non-culprit vessels remains a controversial concern. Although the presence of obstructive lesions in non-culprit coronary vessels is associated with worse short- and long-term outcomes, there is a risk for inappropriate assessment of lesion severity resulting in unnecessary interventions as well as complications.[8] The identification of non-culprit lesions who may benefit of interventional versus conservative strategies of care is still unclear, with reports of similar rates of major adverse cardiovascular events, such as death or myocardial infarction.[9] Observational studies and meta-analysis suggested a possible reduction in clinical events with staged non-culprit lesion PCI.[7,10] However, these studies are limited by selection bias and confounding. Randomized trials have shown reductions in the risk of composite outcomes with non-culprit lesion PCI, with results driven predominantly by the decreased risk of subsequent revascularization with that strategy.[11,12] The Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial was designed to address this evidence gap.[13] This trial showed that, among patients with STEMI and multivessel CAD, a strategy of routine non-culprit lesion PCI with the goal of complete revascularization, performed either during the index hospitalization or soon after discharge, was

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superior to a strategy of culprit-lesion-only PCI in reducing the risk of death from cardiovascular causes or new myocardial infarction, as well as the risk of death from cardiovascular causes, new myocardial infarction, or ischemia driven revascularization, at a median follow-up of 3 years.[13] Moreover, in patients with STEMI and multivessel CAD, multivessel PCI compared with culprit vessel-only PCI was associated with lower risk for reinfarction, with no difference in all-cause mortality. Another parameter to take into account for the revascularization decisions of non-culprit lesion could be the fractional flow reserve (FFR). FFR is the whole-cycle ratio between the hyperemic distal coronary pressure (Pd) and the aortic pressure (Pa) and can be used to determine non-culprit artery alterations in hyperemic coronary flow and microvascular resistance and, consequently, non-culprit lesion revascularization strategies.[14,15] In patients with chronic or acute coronary syndrome without ST-segment elevation, the use of FFR measurement during PCI to assess the functional severity of coronary lesions results in a lower risk of major cardiovascular events than myocardial revascularization guided by angiography.[16,17] The Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial was designed to investigate whether the use of FFR in complete revascularization results in a better clinical outcome than the use of angiography in patients with STEMI and multivessel disease.[18] This trial showed that in patients with STEMI undergoing complete revascularization, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year. However, given the wide confidence intervals for the estimate of effect, the findings do not allow for a conclusive interpretation.[18] The Compare-Acute trial showed that the addition of FFR-guided revascularization of non–infarct-related coronary arteries at the time of primary PCI in patients with STEMI and multivessel disease resulted in a lower rate of a composite cardiovascular outcome that included death from any cause, nonfatal myocardial infarction, revascularization, and cerebrovascular events.[19] This reduction was driven mainly by decreased need for subsequent revascularizations. The Compare-Acute trial also showed that approximately half the lesions in non-infarct-related arteries that were considered to be significant on coronary angiography had an FFR value of more than 0.80 and were therefore not physiologically significant.[19] Bainey et al.[20] in their systematic review and meta-analysis of 10 randomized clinical trials of 7030 unique patients, showed that in those with STEMI and multivessel disease, complete revascularization was associated with a reduction in cardiovascular mortality compared with culprit-lesion-only PCI. There was no differential association with treatment between FFR- and angiography-guided strategies on major cardiovascular outcomes.[20] Despite the solid clinical evidence, FFR is prone to artifacts, may yield inaccurate results, and is under-utilized in practice, in part because of the requisite use of hyperemia which is cumbersome and produces variable clinical responses. FFR also has recognized limitations and is more difficult to interpret in the presence of significant LV dysfunction, diffuse atherosclerosis, microvascular dysfunction and all lesion subset (e.g., chronic total occlusion, calcified lesions, and severely tortuous lesions).[21] In addition to FFR to evaluate functional significance of coronary artery lesions, a noninvasive approach using myocardial perfusion imaging may guide the decision process on revascularization of these lesion.

Radionuclide myocardial perfusion imaging is widely used for noninvasive assessment of stress-induced myocardial ischemia, to rule out the presence of significant coronary stenoses and guide patient's management.[22,23] It has been largely demonstrated in several patient's population that radionuclide perfusion imaging has a strong diagnostic and prognostic power, also in the presence of a negative study.[24–26] In making decisions on revascularization, stress tests are strongly recommended to confirm inducible ischemia because recent clinical trials failed to show the benefits of routine rather than provisional revascularization for stable coronary disease.[27]

In the current issue of the Journal, Karthikeyan et al.[28] conducted an international, randomized, non-inferiority trial comparing ischemia-guided non-culprit vessel angioplasty to routine non-culprit vessel angioplasty, following primary PCI for STEMI (IAEA SPECT STEMI trial). They hypothesized that a strategy of systematic noninvasive assessment of inducible ischemia to guide decisions regarding non-culprit PCI, will be noninferior to routine non-culprit PCI, in reducing ischemia burden. The study included patients over the age of 18, presenting with a first STEMI, had a successful primary PCI, and had a significant stenosis ($\geq$ 70% diameter stenosis) in at least one non-infarct-related coronary artery, or major side branch ($\geq$ 2.5 mm diameter). In all, 109 patients were enrolled from 9 countries. Their results showed that in the ischemia-guided arm, 25/48 (47%) patients underwent non-culprit vessel PCI following stress SPECT myocardial perfusion imaging. In the routine non-culprit PCI arm, 43/56 (77%) underwent angioplasty (86% within 6 weeks of randomization). The median percentage of ischemic myocardium on follow-up imaging (mean 16.5 months) was low, and identical (2.9%) in both arms (difference

0.13%, 95% confidence interval − 1.3–1.6%, $P < 0.0001$; non-inferiority margin 5%). Therefore, they concluded that a strategy of ischemia-guided non-culprit PCI resulted in low ischemia burden and was non-inferior to a strategy of routine non-culprit vessel PCI in reducing ischemia burden. Karthikeyan et al.[28] aimed to clarify the best strategy in patients with evidence of additional non-culprit lesions after STEMI; however, the topic is complex, and some points should be highlighted and discussed. First, Karthikeyan et al.[28] proposed a prospective trial on a limited number of patients, in which the occurrence of COVID-19 pandemic status strongly affected the access to nuclear medicine facilities. This limitation may have affected the results and the lack of differences between non-culprit PCI vs. image guided PCI may be partially related to these factors. Moreover, previous studies demonstrated that the changes in perfusion parameters, obtained early and 6 months after acute myocardial infarction, have a great prognostic impact in predicting long-term outcome.[29] In Karthikeyan et al.[28] investigation, including a mean time between the two imaging studies of 16.5 months, no data on subsequent follow-up are reported. Moreover, despite the amount of ischemia at imaging after revascularization was comparable between routine non-culprit PCI vs. image guided PCI, the authors suggest that selective non-culprit PCI following STEMI offers the potential for cost-savings and may be particularly relevant to low-resource settings. However, if it is more cost-effective to treat non-culprit lesion at the time of initial angiography versus doing an imaging study within 7 days remain to be addressed by a cost-effective study. It should be considered that in patients with multivessel CAD, the identification of those candidates to PCI would results in a more judicious use of stents, improving clinical outcome and decrease healthcare costs. A selective approach has the potential to reduce costs and complications, without adversely affecting outcomes.

Therefore, despite the results from the IAEA SPECT STEMI trial[28] provide encouraging preliminary data in this setting of a selective approach, the benefits of routine revascularization of non-culprit obstructive CAD in STEMI patients remain to be fully addressed. In order to identify the optimal patient centric approach to this dilemma further data are needed. In particular, prospective studies with a larger patient population, an optimal timing for radionuclide imaging and available subsequent follow-up data, have the potential to define if an ischemia-based approach may provide a real benefit on outcome. Moreover, a cost effectiveness analysis will be needed to assure that the care of these patients will provide the highest value possible for the resources consumed. Large prospective randomized trials, with a rigorous study design, performed with new generation cameras allowing to a real savings in terms of costs and exposures,[30] could be the way to answer the question.

## Disclosure

*Valeria Cantoni, Roberta Green, Emilia Zampella, Adriana D'Antonio and Alberto Cuocolo declare that they have no financial conflict of interest.*

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