Imaging phenotypes and outcomes after revascularization in chronic coronary artery disease

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In chronic coronary artery disease (CAD), myocardial revascularization aims at treating myocardial ischemia for symptom relief or to reduce the risk of major acute cardiovascular events including myocardial infarction (MI) and death.[1,2] A meta-analysis has indicated that revascularization targeting functionally significant lesions defined by reduced fractional flow reserve (FFR) reduces the risk of death and MI as compared to medical therapy alone.[3] Similarly, observational studies have found survival benefit from myocardial revascularization over medical therapy in patients with moderate to severe myocardial ischemia on non-invasive testing.[4] However, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) did not find reduction in risk of MI or death between such patients randomized to early invasive or conservative strategy during a median of 3.2 years of follow-up, although symptoms and quality of life improved upon revascularization.[5] Consequently, there has been an increased interest in studying disease phenotypes that might predict prognostic benefit from revascularization in chronic CAD.

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In this issue of the journal, Liga et al. evaluated associations between anatomic and functional severity of CAD, myocardial revascularization, and outcomes in a registry of patients referred to myocardial perfusion imaging and subsequently, had either coronary computed tomography angiography (CTA) or invasive coronary angiography within 90 days.[6] Among 1585 patients, 1184 had obstructive CAD defined as a stenosis of $\geq$ 70% and in 466 patients, obstructive CAD was associated with significant ischemia involving $>$ 10% of the left ventricle. The management of patients with obstructive CAD was classified as appropriate in 797 patients in whom all obstructive lesions associated with significant myocardial ischemia were revascularized or, in the absence of significant ischemia, a conservative strategy was chosen. Management was classified as inappropriate in 386 patients in whom ischemic lesions were not treated (37% of such patients) or revascularization was performed in the absence of ischemia.

The main finding of the study by Liga et al. is that the primary end-point of cardiac death or non-fatal MI occurred less frequently in patients who were treated appropriately versus inappropriately treated.[6] During average follow-up of 4.7 years, 132 patients died or had non-fatal MI. Patients with obstructive CAD associated with significant ischemia had significantly higher event rate when ischemic lesions were not treated versus those who had complete revascularization (17.6% vs 5.1%, $P < .001$). Conversely, revascularization of non-ischemic lesions was not superior to conservative management. Appropriateness of management remained associated with outcomes when adjusted for previous MI, elevated fasting plasma glucose, left ventricular ejection fraction, and extent of ischemia.

In addition to diagnostic performance, clinical value of a diagnostic test depends on its ability to stratify

patients at low or high risk of adverse events and guide subsequent management. The use of either functional imaging or invasive functional assessment for myocardial ischemia is recommended to evaluate stenoses before revascularization.[1] In the study of Liga et al., appropriateness of revascularization was defined based on finding myocardial ischemia involving > 10% of the left ventricle, a subgroup in which revascularization has been shown to be associated with prognostic benefit.[1,4] It should be noted, however, that revascularization may be appropriate in the presence of less extensive ischemia for reducing symptoms rather than for prognostic reasons.

The study of Liga et al. adds to emerging evidence that combined anatomic and functional approach to investigate patients with chronic CAD may guide management for improved outcomes. In this respect, functional information can play a complementary role by further refining cardiovascular risk prediction.[7,8] In the Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease (EVINCI) study, patients with CAD and ischemia who were managed with early revascularization had similar outcomes to patients with CAD without ischemia managed without revascularization.[9] Conversely, patients with CAD without ischemia had higher event rates when revascularized.[9] The Scottish Computed Tomography of the Heart (SCOT-HEART) trial demonstrated that anatomic approach, with coronary CTA, on top of exercise testing decreased rate of nonfatal MI compared to standard care.[10] Observational analysis by Miller et al. found in large, propensity score matched cohorts that revascularization by both percutaneous coronary intervention and coronary artery bypass surgery was associated with reduced all-cause mortality (hazard ratios .70 and .73, respectively) in the presence of ischemia in > 15% of the left ventricle.[11] Similarly, the study by Patel et al. found in propensity adjusted analyses that there was a significant interaction between ischemia and early revascularization.[12] Patients with greater ischemia on ^{82}Rb PET had improved survival with early revascularization.[12] Exploratory analysis suggested a lower ischemia threshold (< 5% of the LV) above which survival benefit is observed with early revascularization than in earlier analyses based on SPECT.[4,11,12] In addition to ischemia, new parameters based on quantification of myocardial blood flow have been evaluated for predicting benefit from early revascularization. One study found that revascularization of lesions associated with severe reduction of coronary flow capacity determined by ^{82}Rb PET was associated with reduced risk of death and myocardial infarction.[13] Other studies have found that reduced global myocardial flow reserve measured by ^{82}Rb PET was a predictor of mortality benefit from revascularization.[14,15]

The analysis of Liga et al. is associated with limitations inherent to retrospective analysis and nonrandomized allocation of management. Despite significant ischemia, relatively large proportion of patients was not revascularized, which may be caused by many reasons, such as uncertainty regarding whether the test results were responsible for the patient's presenting symptoms, patient preference, challenges in performing revascularization or comorbidities. Thus, there may be unmeasured confounding factors impacting survival and risk of MI in unmatched cohorts. However, the study of Liga et al. is representative of all patients evaluated for potential revascularization, whereas patients who did not have a clear equipoise between invasive and conservative strategy, such as those with unacceptable levels of angina, may be less likely to be enrolled in a randomized clinical trial. A comprehensive medical therapy has been part of the management in randomized trials,[1,5] whereas adherence to medical therapy is uncertain in real life. Finally, follow-up was longer in the study of Liga et al. than in the ISCHEMIA trial. These factors may explain differences in the results of the ISCHEMIA trial[5] vs observational studies.[4,6,9,11,12]

The study by Liga et al. provides evidence that combination of significant obstructive CAD and large area of myocardial ischemia is a strong predictor of outcomes that also correlates with benefit from early revascularization. However, due to its observational design, the study does not indicate a causal relationship between revascularization of ischemic myocardium and improved outcomes, because of multiple factors influencing decisions on revascularization. However, observational studies in cohorts representative of all patients being evaluated for CAD complement randomized controlled trials in providing information about the complex relationship between coronary anatomy, revascularization, and outcome in chronic CAD.

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