

ISCHEMIA, to revascularize or not to revascularize

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Management of patients with coronary artery disease is focused on preventing cardiovascular events, improving survival, and control of anginal symptoms, and the cornerstone of treatment is optimal medical therapy with or without coronary revascularization.¹ When these options of therapy have been compared among patients with stable ischemic heart disease, the benefits of coronary revascularization in addition to optimal medical therapy is not as clear as among patients with acute coronary syndrome. This is based on the results of several large randomized clinical trials that have failed to show a consistent superiority of one treatment strategy compared to the other. However, some results from observational studies have suggested that coronary revascularization may be superior to optimal medical therapy among patients with significant ischemia.^{2,3,4,7} The above-mentioned hypothesis served as the nidus behind the ongoing National Heart, Lung, and Blood Institute-funded ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522). In this trial, patients with stable ischemic heart disease and at least moderate ischemia will be randomized to optimal medical therapy with or without coronary revascularization to definitively answer the ongoing dilemma whether an invasive strategy with revascularization improves long-term outcomes in a randomized controlled trial.

Although ischemia can be detected and quantified through multiple modalities, the richest data confirming the role of myocardial ischemia as a strong prognostic factor come from nuclear imaging.^{8–12} In this issue of the journal, Nudi et al reports a single-center, retrospective observational study evaluating the impact of coronary revascularization as compared to medical therapy on ischemia in patients undergoing serial stress- and rest-gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) studies. In order to better evaluate a cohort of patients with stable ischemic heart disease, patients were excluded if they had unstable angina in the prior 6 months, prior myocardial infarction, reduced left ventricular ejection fraction (<45%), or a left ventricular end diastolic volume index > 130 ml/m². Ischemia was semi-quantified by 2 experienced unblinded readers based on previously published (but not widely adopted) seven-region segmentation approach for left ventricular myocardium corresponding to a maximal ischemia score (MIS) group (no, minimal, mild, moderate, or severe ischemia).¹³ The authors identified a total of 3631 patients who underwent serial SPECT MPI between the years of 2004–2014 with 27% ($n = 967$) undergoing coronary revascularization and 73% ($n = 2664$) receiving only medical therapy at baseline. Multivariable adjustment and propensity score methodologies were used to minimize the effect of confounders. Unadjusted analyses revealed that revascularization was more effective than medical therapy in reducing myocardial ischemia in those patients with baseline moderate or greater MIS scores. All adjusted and propensity-matched analyses suggested a lower odds of a unit increase in MIS scores of patients who underwent revascularization as compared to medical therapy alone.

Given the observational nature of this study, several limitations should be noted. First, the study is subject to selection biases based on inclusion criteria and treatment assignment. Although the authors attempted to control for confounding using adjustment methods and

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propensity matching, there were several notable differences between those who were placed on medical therapy and those who received revascularization. This is clearly demonstrated in the propensity-matched analysis where the analytic cohort was reduced from 3631 to 732 patients, and the statistical significance of the results was less pronounced (P dropped from <0.001 for multi-variable-adjusted analysis to 0.042 for propensity-matched analysis). Second, there were several important factors associated with management strategies that were not accounted for (chronic kidney disease, baseline angina status, prior revascularization by type, peripheral arterial disease, financial status, medication compliance), neither in the adjustment or propensity-matched groups. Third, when using propensity methodology, prior work has discouraged the use of statistical significance testing and suggested the use of standardized differences to assess the balance in propensity matching as this measure of distribution is not as sensitive to sample size as traditional testing.^{14,15} Fourth, there was no definition of optimal medical therapy or report of medication dosing, and it is certainly plausible that suboptimal medical therapy could have contributed to changes in ischemic burden on follow-up testing.

In spite of the above-mentioned limitations, the results from this analysis are similar to the prior reported sub-studies from the COURAGE and BARI-2D, which evaluated the effects of medical therapy and revascularization on ischemic burden.^{6,7} In the COURAGE sub-study, patients underwent baseline and follow-up SPECT MPI, and it was found that revascularization in addition to optimal medical therapy resulted in a greater proportion of patients achieving the primary end point of $\geq 5\%$ reduction in ischemic myocardium at follow-up (33% vs 19%, $P = 0.0004$), especially patients among those with moderate-to-severe baseline ischemia (78% vs 52% $P = 0.007$). However, no differences were noted in adjusted death or myocardial infarction rates based on ischemia reduction.⁷ In the BARI-2D sub study, 1-year follow-up SPECT MPI was performed in 1505 diabetic patients with stable ischemic heart disease. It was found that a greater proportion of patients who received revascularization had no ischemia as compared with those assigned to optimal medical therapy (59% vs 49%, $P < 0.001$). Similar to COURAGE, myocardial ischemic severity was not an independent predictor of death or MI after adjustment.⁶

As the ISCHEMIA trial is progressing in a slow fashion, having recruited only 3020 patients out of a goal of 8000 patients as of May 17th, 2016 (<https://www.ischemiatrial.org>; accessed on May 17, 2016), we will have to wait for several more years to better understand the complex interaction between ischemic burden, optimal medical therapy, and coronary

revascularization, and how these factors impact patient outcomes. In the interim, we should continue to follow current practice guidelines¹ along with the Appropriate Use Criteria¹⁶ that have been vetted by the leaders in our field.

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