Response to Letters Regarding Article, “Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden: Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy”

On behalf of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Investigators, we wish to thank Drs Joshi, Tarantini, and colleagues for their letters to the editor regarding our article.1 Many excellent comments were made that serve to clarify the COURAGE nuclear substudy. It is important to note that this study was devised to compare treatment effectiveness using nuclear quantification of ischemia as a surrogate outcome. The design of the substudy was based on the prognostic findings from observational registries of tens of thousands of patients undergoing stress myocardial perfusion single photon emission computed tomography (SPECT).2–4 Importantly, no published data were available previously to suggest that significant relative risk reduction would be seen in patients with ischemia reduction. Therefore, this study was not powered to examine differences in prognosis but was designed to determine whether percutaneous coronary intervention (PCI) resulted in a greater reduction of objective ischemia than did optimal medical therapy alone, extending prior, small series that found serial changes in perfusion induced by an array of antiischemic therapies.5 Thus, the interpretation of clinical outcomes from the COURAGE nuclear substudy should be viewed with caution, especially as risk-adjusted models did not show a prognostic benefit between ischemia reduction and risk reduction. Our preliminary data do suggest that there is potential risk reduction for those patients with significant ischemia reduction (ie, ≥5% of the myocardium) or minimal residual ischemia after intensive medical therapy with or without PCI.

We believe, therefore, that the implication of Tarantini and colleagues that a study focused solely on patients with more extensive and severe ischemia as documented by nuclear imaging has merit. These authors suggested that had we limited enrollment to only patients with moderate-to-severe ischemia and lifestyle modifications and antiischemic therapeutic regimen with or without PCI. Finally, it is worth emphasizing that, with only a few prespecified exceptions, patients in the COURAGE trial were required to demonstrate objective evidence of ischemia; however, myocardial perfusion SPECT was not a prerequisite for enrollment, thereby accounting for the small size of the substudy.

Joshi notes an important potential interrelationship between regional perfusion ischemia and left ventricular function. COURAGE nuclear patients had an average ejection fraction of 57%, with few patients having marked systolic dysfunction. Additional stratification by left ventricular function and ischemia within the current cohort results in patient subsets that are too limited in size. Thus, further investigation as to the value of both parameters in larger, adequately powered cohorts will provide important clues as to how to further improve secondary prevention of stable angina patients. This substudy complements prior work,5 providing compelling evidence to suggest that quantitative stress myocardial perfusion SPECT imaging may be an important determinant of outcome in the context of therapies as varied as PCI and optimal medical therapy. Coronary disease patients with chronic stable angina and demonstrable SPECT ischemia exhibit marked improvements in symptom status as a result of an aggressive secondary prevention strategy with and without PCI. Thus, we hope that the COURAGE nuclear substudy may spawn additional investigations that will assess the value of ischemia-guided therapeutic decision making. It remains possible, if not likely, that although the COURAGE main trial results were nonsignificant (P=0.62), future trials focusing on higher-risk patients with more left ventricular dysfunction and more ischemia may find benefit from revascularization. What has been learned from both the main trial and nuclear substudy is that intensive medical therapy is safe and can result in a sizable reduction in ischemic burden for patients with chronic stable angina. We look forward to future trials to determine whether quantitatively analyzed extensive myocardial ischemia identifies a subset of patients with stable coronary artery disease who benefit from coronary revascularization, thereby providing a useful guide to a critical decision point in the management of patients with chronic stable angina.

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Disclosures

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