ISCHEMIA trial update

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As originally described in the *American Heart Journal*,[1] the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial has randomized patients with moderate or severe ischemia to an early invasive or conservative treatment strategy. The primary goals of treating patients with stable ischemic heart disease are to avoid disease progression and to improve their health status: their symptoms, function, and quality of life. Accordingly, the primary disease progression outcome is a 5-component composite clinical outcome (cardiovascular death; myocardial infarction; or hospitalization for unstable angina, resuscitated cardiac arrest, or heart failure), the key secondary outcome is patients' self-reported health status.

In the original study protocol and in the description of the study in the *American Heart Journal*, the health status analysis plan was to focus on angina symptoms and angina-related quality of life, as measured by the Angina Frequency and Quality of Life Scales from the Seattle Angina Questionnaire (SAQ).[2] Subsequent to funding of the ISCHEMIA trial, a shortened, 7-item version of the SAQ was introduced that not only reduced the response burden of the SAQ but also introduced a Summary Score that integrates patients' symptoms, function, and quality of life into a single score that ranges from 0 (the worst health status) to 100 (no angina, no physical limitations, and no angina-related impacts on patients' quality of life).[3] Because the SAQ Summary Score integrates all of the disease-specific impacts of coronary artery disease on patients' health status, we are altering the original analytic plan to have the SAQ Summary Score, as acquired by the Brief Symptom Survey (7-item SAQ) collected throughout study follow-up, serve as the primary health status outcome and the key secondary end point of the ISCHEMIA trial.

The advantages of using the SAQ Summary Score as the primary measure of the health status benefits are that a single primary end point comparison, rather than 2 (thus eliminating concerns some may have about multiple comparisons), and a more holistic (patient-centric) interpretation of treatment effectiveness can be gained. The individual SAQ Angina Frequency and Quality of Life scores will still be reported as secondary outcomes to better explain and describe the main health status results. This change was agreed upon by study leadership with approval of both the National Heart, Lung, and Blood Institute and ISCHEMIA's Data and Safety and Monitoring Board. In addition, a key subgroup analysis will be to stratify the ISCHEMIA results among those with daily/weekly angina (baseline SAQ Angina Frequency score ≤60), monthly angina (SAQ Angina Frequency score 61-99), and no angina (SAQ Angina Frequency score = 100) at randomization, as there is a strong, clinically logical reason to hypothesize that the greatest benefits of an invasive approach would be in those with more frequent baseline angina and little benefit would be expected in those who were asymptomatic. These changes were made prior to the planned database lock date of September 30, 2019, and before unblinding of the data.

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References

1. Group ITR. Maron DJ, Hochman JS, O'Brien SM, Reynolds HR, Boden WE, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. Am Heart J 2018;201:124-35.
2. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25(2):333-41.
3. Chan PS, Jones PG, Arnold SA, et al. Development and validation of a short version of the Seattle angina questionnaire. Circ Cardiovasc Qual Outcomes 2014;7(5):640-7.

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