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CARDIOVASCULAR PERSPECTIVE

ISCHEMIA: Establishing the Primary End Point

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Intelligence is the ability to adapt to change
—Stephen William Hawking (1942–2018)

The ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522) is a National Heart, Lung, and Blood Institute (NHLBI)–funded randomized, comparative effectiveness trial testing the incremental value of an invasive strategy of cardiac catheterization and revascularization (if suitable) when added to optimal medical therapy in patients with at least moderate ischemia on stress testing and symptoms controllable with antianginal medication, as compared with an initial strategy of optimal medical therapy with cardiac catheterization reserved for failure of medical therapy. The trial successfully completed enrollment in January 2018 and is currently in the follow-up phase. Herein, we provide the rationale for choosing the trial's primary and key secondary end points and the processes leading to their ultimate selection.

PRIMARY END POINT PLANNING IN ISCHEMIA

The ISCHEMIA grant application, funded by NHLBI in 2011, designated a 5-component primary end point consisting of cardiovascular death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.[1] The trial was designed to optimize precision around point estimates for important clinical outcomes, to inform shared decision-making between patients and clinicians guided by robust data on the risks and benefits of alternative therapies for a common condition. After the award, we sought and received approval from the study's data safety monitoring board, which was charged with protocol review, and the NHLBI to change the primary end point to cardiovascular death or MI, with a contingency plan clearly articulated in the protocol before its final approval to switch back to the 5-component end point to retain power if an insufficient number of primary end point events accrued at a designated time point during the trial (before accrual of 75% of end point events). This contingency plan was developed to avoid a common pitfall of other trials, namely lower than projected power because of lower than projected event rates. An event-driven trial was considered as an alternative but was not possible because the duration of follow-up and thus costs would be uncertain. The plan to adopt the 5-component primary end point if total aggregate events were accruing at a lower than expected rate was approved by the DSMB in 2011 and included in the original protocol in January 2012 prior to the start of patient enrollment.

The projected primary end point event rate used in power calculations during the trial's design phase was based on multiple data sources, including the COUR-

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AGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) nuclear substudy[2] and several stress imaging registries. Although we believed that the projected rate was conservative (20% at 4 years in the conservative group), we recognized that precision around estimates in the literature was wide, that the ISCHEMIA end point definitions were more stringent than in the studies from which estimates were derived, and that participants enrolled in clinical trials tend to have lower event rates, in part, because of advances in medical therapy. In this regard, it is not uncommon for large clinical trials to have lower than anticipated event rates, and any changes to the primary end point during the trial should be prespecified, similar to what was done in ISCHEMIA.[3]

WHEN AND HOW WAS THE CONTINGENCY PLAN ACTIVATED?

The contingency plan in the trial protocol, which has not changed since 2012, specified that an NHLBI-appointed Advisory Panel, independent from the data safety monitoring board (as they would have access to unblinded data) would be convened by NHLBI (if needed) for the purpose of reviewing unconditional power estimates and making a recommendation to the NHLBI regarding the need for protocol modifications to preserve trial power. Members of this panel would not have access to unblinded data by treatment group or other data that might bias their recommendation.

Projections in 2015, using updated assumptions for the randomization rate, suggested that the initially planned 8000 randomized participant sample size would not be reached, and concurrent accruing data suggested that the observed rate of inappropriate cardiac catheterization in the conservative strategy arm was substantially lower than projected. A formal request to reduce the randomization target to 5000 was accepted by NHLBI in 2016. The first analysis to project the final aggregate number of primary end point events was conducted in 2016, blinded to treatment group. Based on the pooled aggregate event rate at that time, in concert with revised recruitment projections, study leadership determined there was a need to discuss activation of the contingency plan with the Steering Committee and investigators. In 2016, the projected need to increase the power by extending follow-up and reverting to the 5-component end point as the primary end point was discussed at Steering Committee and Investigator meetings and communicated to participating sites.

The Independent Advisory Panel was convened by NHLBI in May 2017. Panel members were chosen based on their expertise in clinical trials and having had no role in the design or conduct of the ISCHEMIA trial. The Independent Advisory Panel was presented with power and precision estimates for the 2-component and 5-component end points calculated using a range of assumptions about the extension of enrollment and follow-up[4] and incorporating event rate estimates derived from blinded review of the aggregate accruing study data.[5] The Independent Advisory Panel explicitly discussed the concern that the 5-component composite may be regarded as a softer end point. After weighing these various options, the Independent Advisory Panel recommended to NHLBI and study leadership that the primary end point be reverted to the original 5-component composite end point and that the 2-component composite end point be retained as a key secondary end point, in addition to extending follow-up. In June 2017, study leadership and NHLBI accepted the panel's recommendation, which was communicated to the Steering Committee and Investigators at August and November 2017 in-person meetings and by e-mail to all participating sites.

IS THE CURRENT PRIMARY END POINT CLINICALLY IMPORTANT?

The choice of a primary end point for a large clinical trial should be based on a variety of considerations, including expected event rates, importance to patients, sensitivity to intervention, and susceptibility to bias in ascertainment and reporting. All-cause mortality is undoubtedly the most relevant, unbiased single end point. Unfortunately, the sample size required to detect a difference in all-cause mortality in the stable ischemic heart disease population receiving optimal medical therapy enrolled in ISCHEMIA would have been prohibitively high. Even though ISCHEMIA randomized 5179 participants, more than the sum of participants randomized in the COURAGE and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trials, it was not adequately powered for a primary end point of all-cause mortality, which would have required a sample size of 11 656 patients (80% power for a 20% risk reduction). Power can be increased by extending the duration of follow-up, and we hope to be funded to execute the plan proposed in the protocol to extend duration of follow-up for several years after completion of the currently funded phase of the trial to assess all-cause mortality.

During the design of the trial, the study team had extensive discussions about which events were the most relevant to add to cardiovascular death or MI for a composite end point. Unstable angina was selected because it is clinically relevant, has quality of life and economic impact, and because revascularization has the potential to reduce unstable angina by reducing the frequency and extent of ischemia. However, a clinical diagnosis of

Table. Definition of Hospitalization for Unstable Angina in FAME 2 and ISCHEMIA

FAME 2	ISCHEMIA
Unplanned hospitalization leading to an urgent revascularization procedure	Hospitalization for unstable angina
Patient is hospitalized unexpectedly because of persisting or increasing complaints of chest pain (with or without ST-T changes), and a revascularization is performed within the same hospitalization.	Prolonged ischemic symptoms at rest (usually ≥10 min in duration) or accelerating pattern of chest pain that occurs with a lower activity threshold (Canadian Cardiovascular Society class III or IV) considered to be myocardial ischemia on final diagnosis resulting in an unscheduled visit to a healthcare facility resulting in an overnight stay generally within 24 h of the most recent symptoms, cardiac biomarkers not meeting MI criteria, and at least 1 of the following:
	A. New or worsening ST or T-wave changes on resting ECG* (core laboratory assessed) B. Angiographic evidence of a ruptured/ulcerated plaque or thrombus in an epicardial coronary artery believed to be responsible for the ischemic symptoms/signs (core laboratory assessed).

FAME 2 indicates Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2, ISCHEMIA indicates International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; and MI, myocardial infarction.

*ECG criteria: ST-segment shifts and T-wave changes: new horizontal or downsloping ST depression ≥0.05 mV in 2 contiguous leads and T inversion ≥0.1 mV in 2 contiguous leads or new ST-segment elevation ≥0.1 mV in 2 contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis, such as left bundle branch block, left ventricular hypertrophy with repolarization abnormalities, preexcitation, and pacemakers.

unstable angina is subject to ascertainment and reporting bias by unblinded investigators and patients. Hence, unstable angina was defined strictly (Table) and adjudicated centrally (see ascertainment bias mitigation measures below). Resuscitated cardiac arrest, defined as successful resuscitation for documented cardiac arrest, may be caused by severe ischemia; therefore, risk for this end point may be reduced by revascularization. Hospitalization for heart failure was chosen as a component of the primary end point because of its strong relationship with stable ischemic heart disease, its impact on subsequent mortality in other cardiovascular trials, and because of the pathophysiologic link between repeated ischemic or injury events and ischemic cardiomyopathy. Consequently, revascularization for extensive ischemia could theoretically prevent the development of heart failure.

Although we recognize that some of these end points are not as hard as cardiovascular death or MI, unstable angina and heart failure hospitalization are valid and clinically important outcomes in a trial designed like ISCHEMIA for the following reasons:

1. Patients were randomized before cardiac catheterization. This is a critical design feature that distinguishes ISCHEMIA from COURAGE, the BARI 2D trial, and the FAME 2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) study, in which participants were randomized with full knowledge of their coronary anatomy. During the design phase of the trial, it was felt that knowledge of coronary anatomy could have led to exclusion of high-risk subsets in these earlier trials. Moreover, knowledge of coronary anatomy can increase the risk of ascertainment bias among providers and patients, potentially increasing reported events and crossovers in participants randomized to a conservative strategy; although being masked to anatomy reduces the risk, it does not eliminate it.
2. Bias in the ascertainment of events is mitigated by carefully constructed data collection that focuses sites on end point events, screening of ECG and angiographic core laboratory data for possible events, including core laboratory-reviewed routine 2-year ECGs, site investigator and coordinator education about the importance of event reporting, use of triggers/queries and algorithms programed to capture potential missed events (eg, cardiac biomarker elevation; hospitalization for other reasons, including chest pain, dyspnea, or pneumonia; and New York Heart Association class IV or Canadian Cardiovascular Society class IV on study visits), and request for information on potential events found during review of source documents. In addition, methods are used to ensure reporting of hospitalizations, including periodic review of medical records by site coordinators, review of national, regional, or health insurance databases (where available), cross-checking of US medical bills against reported hospitalizations and, at selected sites, monitoring visits with medical record review. The open-label OAT (Occluded Artery Trial)[6] also included hospitalization for heart failure in the primary end point and demonstrated no evidence of ascertainment bias, with no between-group differences. During the conduct of ISCHEMIA, site variation in anticipated versus observed event reporting has been reviewed. Sites with low reported event rates had additional monitoring (including on-site monitoring). No concerns have been identified thus far based on these efforts, but this will continue to be carefully monitored.
3. Patients with high levels of angina at baseline—a main driver for treatment crossovers from a conservative strategy—were excluded from randomization, thereby limiting the potential effects of participants' residual biases about revascularization on the hospitalization for unstable angina end point.

4. Although not directly mitigating reporting bias, the ISCHEMIA definitions of these end points include objective criteria that are more stringent than the recent Food and Drug Administration Panel recommendation.[7] For example, the Table compares the criteria for unstable angina hospitalization from FAME 2[8] with those of ISCHEMIA. The ISCHEMIA criteria not only require symptoms and hospitalization but also objective ECG criteria that must be read and confirmed by the ECG core laboratory, or specific angiographic findings confirmed by the angiographic core laboratory. Events that do not have ECGs available for core laboratory review or do not show specified changes are not confirmed as unstable angina. Similarly, the definition of hospitalization for heart failure requires all of the following: hospitalization for symptoms and physical signs of heart failure and need for additional or intensified therapy for heart failure.
5. The end points are adjudicated centrally by a Clinical Events Committee blinded to assigned treatment strategy.

Reporting bias because of anxiety related to not receiving a desired treatment is a real phenomenon but is complex because of the nature of patients' symptoms and the wide range of patient preferences. Furthermore, the desired treatment may differ between patients and providers. For example, in the OAT trial, the most common reason for patient refusal to participate was preference for conservative management, whereas physician refusals were mainly because of their bias toward invasive strategy.[9]

The end point cardiovascular death or MI is a key secondary end point for ISCHEMIA and remains of major importance to all stakeholders. Of note, based on aggregate accrued data, the trial is projected to have 80% power to detect a 20% reduction in the 2-component end point. However, only all-cause mortality is truly incontrovertible. Numerous definitions of MI are in widespread use (especially for procedure-related events), and ascertainment bias may affect the assessment of MI events. Such bias is minimized in ISCHEMIA by protocol-driven biomarker and ECG assessments and rigorous use of prespecified MI definitions by the Clinical Events Committee, with components of the MI definition requiring confirmation by the ECG or angiographic core laboratories.

As we stated in our letter to the Editor,[10] The ISCHEMIA trial has been conducted in accordance with the most rigorous clinical trial standards. The process described above to change the primary end point was deliberate and carefully considered, involving the trial Leadership Committee, Steering Committee, National Heart, Lung, and Blood Institute program staff, statisticians, and independent experts; it took nearly a year of planning. As leaders of this NHLBI-funded trial, we take seriously the humbling responsibility granted to us to conduct this trial, and we are confident that the wealth of trial data, the rigor with which it is collected, and our careful adherence to standards in the conduct of clinical trials will substantially advance our knowledge about the management of patients with stable ischemic heart disease and at least moderate ischemia.

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