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Response to Letter Regarding Article “Initial Invasive versus Conservative Management of Stable Ischemic Heart Disease Patients with a History of Heart Failure or Left Ventricular Dysfunction: Insights from the ISCHEMIA Trial”

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In our analysis of patients with heart failure and/or left ventricular dysfunction (HF/LVD), we reported lower rates of the composite of cardiovascular death, myocardial infarction (MI), or hospitalization for unstable angina, HF, or resuscitated cardiac arrest, and secondary outcome (cardiovascular death or myocardial infarction) in patients assigned to the invasive strategy as compared with the conservative strategy¹. Dr. Morgan and colleagues correctly point out that our results were driven by a small number of patients with left ventricular dysfunction (ejection fraction [EF] <45%) in the HF/LVD group, and we agree that these findings should be interpreted with caution.

Our decision to use EF <45% to determine LVD was deliberated extensively and pre-specified in the statistical analysis plan. ISCHEMIA was designed more than 10 years ago when an EF cut-off of 50% was not a consensus. In addition, LVEF thresholds to define heart failure with preserved EF (HFpEF) have been heterogeneous across landmark studies². I-PRESERVE, TOPCAT, and PARAMOUNT, for example, used EF >45% to define heart failure with HFpEF. Additionally, PARAGON, the largest HFpEF trial ever done also used a cut-off of 45% to define HFpEF. Finally, when the specific EF was not available, it was also collected in categories of 55%, 45–54%, 35–44%, and EF<35%. Therefore, using a cutoff of 45% or 55% required the fewest assumptions with imputation. We agree that a LVEF threshold of 50% is currently a widely used cut-off to distinguish HFpEF from HF with moderately reduced EF. We performed a sensitivity analysis using the current guideline threshold of EF >50% to define HFpEF and found similar results. Importantly, instead of dichotomizing EF, our main analysis used EF as a continuous variable, which is the most informative method to analyze this type of data.

As Morgan and colleagues also point out, ISCHEMIA was designed to study patients without significant LVD³, but since 7.7% of patients randomized had HF/LVD, our study

was a unique opportunity to explore the treatment effect of an invasive strategy in such patients with moderate or severe ischemia. We did not further explore the benefit of coronary artery bypass graft surgery or percutaneous coronary intervention as revascularization modalities, but look forward to the results of future studies.

Finally, it is known that patients with LVEF <35% or NYHA III or IV derive long-term benefit after initial increased risk from revascularization with coronary artery bypass surgery with a 16% reduction in death at 10 years⁴. However, less is known about patients with heart failure and/or low LVEF who are treated with percutaneous coronary intervention. Therefore, we look forward to the results of the REVascularisation for Ischaemic Ventricular Dysfunction- British Cardiovascular Intervention Society-2 (REVIVED-BCIS-2) trial⁵, which will help further inform this field.

Disclosure Statement

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Dr. David J. Maron reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study.

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