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REPLY: Interpreting the Impact of Complete Revascularization in the ISCHEMIA Trial

We appreciate the interest in our study from ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches).[1] Dr Dayan and colleagues and Drs Guyton and Halkos question the low complete revascularization (CR) rate after coronary artery bypass grafting (CABG). CR after CABG has traditionally been defined as placement of a graft in each diseased territory,[2] a method that underestimates the rate of incomplete revascularization. In contrast, we required grafting of all diseased vessels with diameter ≥2.0 mm including side branches, not just the parent vessel, and used a sophisticated CR analysis methodology that accounts for retrograde flow from grafts that may not revascularize all proximal diseased zones.[3] ISCHEMIA was not designed to compare CABG and percutaneous coronary intervention (PCI); CABG was reserved for much more complex CAD. In this regard, the ratio of CABG to PCI procedures was similar in ISCHEMIA as in global use in unselected CAD patients. The reported rates of CR after CABG were lower in prior nonrandomized CABG studies without a PCI arm necessitating less complex anatomy for equipoise than in randomized trials.[4] The present study demonstrates that the true CR rate in an unselected CABG population reflective of real-world use is lower than generally appreciated, although it is still higher than with PCI after accounting for disease complexity.[1] Guyton and Halkos further question the ISCHEMIA CR definition. However, they confuse the standard-of-care procedural *strategy* (which varies for PCI and CABG) with the CR *assessment methodology* that was developed specifically for ISCHEMIA to provide independent core laboratory-derived CR assessment with the same criteria for both procedures.[3] This definition was not based on the smallest available stent size, because vessels smaller than 2.0-mm diameter can be treated with either 2.0-mm stents or balloon angioplasty alone. Finally, we see no reason to exclude single-vessel disease from CR assessments or to not perform exploratory post hoc analyses (notwithstanding the fact that the present CR analysis was prespecified).

We agree with Dr Dimitriadis and colleagues that identifying specific phenotypes that benefit from CR is important; this was beyond the scope of the present study. Regarding their second point (also raised by Dr Kaul and colleagues), we do not feel that ISCHEMIA is the proper vehicle to assess the impact of CR separately after PCI and CABG. Invasive (INV) vs conservative (CON) randomization was not stratified by revascularization choice, and assessing the impact of CR with each modality vs CON would have limited power, especially for CABG. Such analyses would be better performed from dedicated trials of PCI vs CON, CABG vs CON, or PCI vs CABG, in which the anatomy is known before randomization. Third, we agree that the greater reduction in cardiovascular death or myocardial infarction (CVD/MI) with anatomic compared with functional CR supports the potential benefit of revascularizing nonflow-limiting high-risk vulnerable plaques,[5] a hypothesis being tested in at least 5 ongoing randomized trials.

Finally, Kaul and colleagues question the lack of multiplicity adjustment given prior ISCHEMIA substudies; selective reporting of 4-year event rates; nonsignificance of the CR treatment effect within the INV group after multivariable adjustment; and the borderline significance of the ∼1% incrementally greater reduction with anatomic CR-INV vs CON compared with all-INV vs CON. In response, we note that no trial, including ISCHEMIA, has ever been designed or powered to determine the impact of CR in stable CAD. However, as the most comprehensive analysis of its type (and the only one with a CON comparator group), we do believe the present exercise is informative. In contrast to most prior CR studies, we adjusted for baseline features in the INV group, which showed attenuation of its effect. Also, there were only 1,801 INV patients available for anatomic CR assessment, further limiting power. Nonetheless, the adjusted "nonsignificant" HR for reduced CVD/MI of 0.76 (a 24% reduction) is plausible and is consistent with prior outcomes.[4] Similarly, the contracted size of the CR cohorts from inverse probability weighting resulted in a widened 95% CI around the observed 3.5% reduction in CVD/MI with anatomic CR-INV vs CON compared with the 95% CI around the 2.4% difference in CVD/MI with all-INV vs CON in the entire study population, further affecting power. We emphasized 4-year event rates (the latest time at which most patients had follow-up); however, the results with CR were similar or better with longer-term follow-up (see Supplemental Tables 26-29 in our paper).[1] Most importantly, we presented these findings as hypothesis-generating, representing associations and not causality, derived from subgroup data analyzed by multivariable and inverse probability weighting modeling, without adjustment for multiple comparisons. Nonetheless, from a Bayesian

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perspective (an approach Dr Kaul highly values), the net sum of evidence from the present and multiple prior informative studies collectively strongly supports the take-home message that the outcomes of an INV approach in stable CAD can be modestly improved if anatomic CR can be safely achieved.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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