Journal of the American Heart Association

EDITORIAL

# Beyond the ISCHEMIA Trial: Revascularization for Stable Ischemic Heart Disease in Patients With High-Risk Coronary Anatomical Features

Brian A. Bergmark, MD; David A. Morrow, MD, MPH

One of the most pressing aspects of the management of patients with stable ischemic heart disease (SIHD) is weighing the risk/benefit trade-off for coronary revascularization. This shared decision with the patient has been framed by the clinical intent of revascularization (survival benefit versus symptom management), cardiovascular risk modifiers (eg, ejection fraction and diabetes mellitus status), and the severity of coronary atherosclerosis. Landmark randomized trials have enhanced our understanding of the role for coronary revascularization in patients with SIHD,[1–7] but questions remain. Now-historical trials of surgical coronary revascularization demonstrated a survival benefit compared with medical therapy in patients with 3-vessel coronary artery disease (CAD) or significant left main CAD. However, contemporary randomized trials of principally percutaneous revascularization have not shown a difference in survival compared with optimal medical therapy, even among patients with moderate to severe ischemia on functional imaging, including patients with 3-vessel disease involving the left anterior descending artery. Nonetheless, patients with left main CAD were excluded from these trials, and there remains a possibility of selection pressures having limited enrollment of patients with complex 3-vessel CAD.[7] Therefore, for some clinicians, there is lingering uncertainty whether coronary revascularization might reduce the incidence of myocardial infarction (MI) or death in patients with severe CAD.

See Article by Bainey et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*),[8] Bainey and colleagues address this question in a nonrandomized, observational analysis from the APPROACH (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease) registry database, which includes data from 2002 to 2016 from the 3 cardiac catheterization laboratories in Alberta, Canada. Paired with additional public data sources to capture long-term patient outcomes, the authors examined clinical outcomes, comparing initial management strategies in 9016 patients with suspected SIHD referred for coronary angiography and found to have high-risk coronary anatomical features.

## WHAT DID THE INVESTIGATORS OBSERVE?

High-risk coronary anatomical features were defined as angiographically defined stenoses ≥70% in

**Key Words:** Editorials ■ coronary artery bypass graft surgery ■ percutaneous coronary intervention ■ revascularization ■ stable coronary artery disease

Correspondence to: Brian A. Bergmark, MD, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Rd, Suite 7022, Boston, MA 02115. E-mail: bbergmark@bwh.harvard.edu



For Disclosures, see page 4.



*JAHA* is available at: www.ahajournals.org/journal/jaha

all 3 epicardial arteries or left main disease ≥50%. Patients were categorized as having undergone revascularization if percutaneous coronary intervention or coronary artery bypass graft surgery was performed within 3 months of the index coronary angiogram. The primary end point of interest was the composite of death or MI. The median follow-up time was 6.2 years. The association between treatment strategy and outcomes was assessed using a Cox proportional hazards model with adjustment using inverse probability of treatment weighting (IPTW) to help account for baseline differences between the groups.

In total, 61% of patients underwent coronary revascularization within 3 months of the index coronary angiogram, 2175 by percutaneous coronary intervention and 3312 by coronary artery bypass graft surgery. The principal observation from this analysis was that patients who underwent revascularization had lower rates of the composite end point (2.7% versus 6.8%; hazard ratio [HR], 0.62; 95% CI, 0.58–0.66), with consistent associations for percutaneous coronary intervention (HR, 0.64; 95% CI, 0.59–0.70) and coronary artery bypass graft surgery (HR, 0.61; 95% CI, 0.57–0.66). Patients who underwent revascularization also had lower rates of all-cause death and cardiovascular mortality individually. There was a statistically significant interaction between these observations and coronary anatomical subgroup, with the strongest associations among patients with severe (≥70%) left main disease (HR, 0.29; 95% CI, 0.19–0.45) or 3-vessel disease with a proximal left anterior descending artery stenosis ≥95% (HR, 0.42; 95% CI, 0.33–0.54).

Cardiovascular medication prescription information was available for a subset of 4974 patients at 6 months.

Although patients who were revascularized had higher rates of use of lipid-lowering agents, β-blockers, and $P2Y_{12}$ inhibitors, adjustment for these differences did not significantly alter the major findings.

## WHAT HAVE WE LEARNED?

Bainey et al have addressed a timely topic central to the management of patients with SIHD. The population studied was at high risk for events and inclusive of some subgroups not well represented in contemporary randomized trials. The investigators have carefully performed analyses aiming to mitigate the unreconcilable confounding attributable to selection bias that is inherent in this observational analysis. Their observations raise thought-provoking hypotheses for these anatomical subgroups.

The absolute event rates reported herein are notable. The aggregate rate of death or MI was ≈4% at 1 year, reinforcing the high-risk nature of this anatomical cohort. These rates are even higher for patients with severe (≥70%) left main disease, who had a 1-year rate of death or MI as high as 11.8% among those managed medically (3.0% among those who received revascularization). Although the absolute rates in individual treatment cohorts to some degree reflect underlying comorbidities and confounding, they nonetheless highlight the concerningly high event rates of these high-risk subgroups.

This analysis from the APPROACH registry is to be interpreted in conjunction with the ISCHEMIA (International study of comparative health effectiveness with medical and invasive approaches) trial,[1] which enrolled patients with SIHD and moderate or severe ischemia on stress testing. Coronary computed tomography angiography was performed in most patients to exclude left main or nonobstructive CAD. Qualifying patients were randomized to a strategy of intended revascularization, which was to occur within 30 days, versus a strategy of optical medical management. Of the 5179 patients enrolled, 79% in the revascularization strategy group and 21% in the optimal medical therapy group underwent revascularization during the trial. The rate of the composite end point of death from cardiovascular causes, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest did not differ between trial arms at 5 years, although patients assigned to an invasive strategy had a greater improvement in symptoms. Patients randomized to an invasive strategy had an early imbalance in procedural MI followed by lower rates of spontaneous MI compared with medically managed patients.

How does the cohort studied by Bainey and colleagues compare with the ISCHEMIA trial population? First, the ISCHEMIA trial excluded patients with left main CAD. In the ISCHEMIA trial, 45% of patients had 3-vessel disease that was defined by ≥50% stenosis. By these criteria, Bainey's analysis cohort from the APPROACH registry had greater severity of coronary atherosclerosis, with all patients having angiographically significant left main (≥50%) or 3-vessel disease at a more stringent threshold of severity (≥70%). The results of functional testing for ischemia were not reported in the APPROACH registry. Angiographic assessment of lesion severity in the intermediate range correlates poorly with functional significance,[9,10] and although we know that irrespective of angiographically defined coronary anatomical features 45% of patients in the ISCHEMIA trial had severe ischemia on stress testing, we do not know the cumulative physiological impact of the coronary disease in the APPROACH registry. Nevertheless, by angiographic criteria, the patients included in the report by Bainey et al reflect a higher-risk coronary anatomical cohort than those enrolled in the ISCHEMIA trial.

In the ISCHEMIA trial, although there was no statistically significant interaction between treatment strategy and the extent of coronary disease, defined at the relatively inclusive threshold of 50% stenosis, there were trends toward treatment benefit with revascularization among patients with severe ischemia on stress testing, 3-vessel disease, or proximal left anterior descending artery disease.[1] For example, in patients with 1-vessel disease, the difference in event rate with an initial invasive management versus conservative strategy was 1.4% (95% CI, −4.1% to 7.1%), showing a trend toward a higher event rate with invasive therapy, versus −3.2% (95% CI, −9.5% to 3.2%) in those with 3-vessel disease, favoring the direction toward revascularization. As such, for some experts, uncertainty remains about the potential benefits of initial revascularization in the population with left main disease or severe 3-vessel disease, as defined by Bainey and colleagues, a cohort who had a higher absolute mortality rate at 1 year in the APPROACH registry (3%) than that seen in the ISCHEMIA trial (1%).

Considering patients with left main CAD, the data from randomized trials supporting revascularization compared with medical management for patients with SIHD are dated and pertain largely to coronary artery bypass graft surgery as the mode of revascularization.[11,12] Yet, given guideline recommendations for revascularization in these patients[13] along with trends in real-world practice reflecting widespread use of revascularization compared with medical therapy in patients with left main CAD,[14] it is not likely that there will soon be a randomized trial of revascularization versus medical management in this anatomical subgroup. Moreover, although the ISCHEMIA trial did increase the overall degree of severity of CAD studied compared with the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial,[6] the especially high-risk patients with severe 3-vessel disease studied by Bainey et al may not have been included. Additional analyses based on more detailed anatomical subsets in the ISCHEMIA trial as well as long-term follow-up may be forthcoming and useful to addressing this question.

## LIMITATIONS OF THIS ANALYSIS

Interpretation of the data from Bainey's analysis of the APPROACH registry must be made in the context of their limitations. Most critically, this analysis was not based on a randomized comparison and the selection by treating physicians and patients of one treatment strategy or another is inherently and deeply confounded. Patients who were managed conservatively were older and had higher rates of comorbidities. Moreover, evidence-based secondary preventive therapies were used more commonly in the cohort who underwent revascularization. Furthermore, many of the patients in the study population had an indication for revascularization according to the European Society of Cardiology guidelines relevant during the study period, which give a class 1A recommendation for revascularization in the setting of left main CAD >50% or proximal left anterior descending artery disease >50%.[13] Therefore, specific clinical considerations presumably led to the deferral of their revascularization.

It is worthwhile to recognize the strengths and limitations of an IPTW analysis. Weighting patients inversely to their likelihood of receiving a certain treatment (IPTW), as was done in the current report, has the potential to lessen treatment-selection bias confounding, but also creates challenges to interpretation. Patients' baseline variables are used to create scores that quantify the likelihood, or propensity, for a given patient to receive one treatment or the other when analyzing nonrandomized observational data. For example, a young patient with severe left main disease and few comorbidities would have a high propensity for undergoing revascularization, whereas an elderly patient with severe kidney disease would be more likely to be managed medically. In an IPTW approach, patients who have a high propensity for one treatment strategy but in fact were treated with the opposite strategy are weighted more heavily than are patients who received the most likely treatment given their clinical profiles. Some argue that this approach reduces confounding with the idea that if a patient was expected to receive treatment A but actually received treatment B, it is almost *as if* that patient had been randomized to treatment B.[15] Conversely, others argue that this approach overweights the unusual cases with the most confounding. Take, for example, a 55-year-old otherwise procedurally low-risk man with severe left main disease who does not undergo revascularization: it is almost certainly not random that the patient or treating heart team decided to defer revascularization. His eventual outcome may reflect an important clinical factor not captured in the database and propensity score, such as a new cancer diagnosis. Although IPTW attempts to account for confounding, it is not a substitute for evidence based on randomized clinical trials for making causal inferences.

## SUMMARY

In summary, Bainey and colleagues have performed well-designed analyses from a robust data set pertaining to an important and understudied subset of patients with SIHD. They have reinforced the high-risk nature of patients with left main or severe 3-vessel CAD and, in

a propensity-weighted, nonrandomized observational analysis, have found a significant association between revascularization and lower rates of adverse outcomes in these patients. Revascularization for left main CAD, specifically in patients with SIHD, has not been investigated in a contemporary randomized trial, and there remains debate about the representation of severe multivessel disease. Bainey et al have drawn attention to an incompletely resolved issue in the management of SIHD.

## ARTICLE INFORMATION

### Affiliations

From the TIMI (Thrombolysis in Myocardial Infarction) Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

### Disclosures

Dr Bergmark reports grant support: Pfizer, AstraZeneca, and Abbott Vascular; and consulting fees: Philips, Abbott Vascular, Servier, Daiichi-Sankyo, Janssen, and Quark. Dr Morrow reports consulting fees: AstraZeneca, Bayer Pharma, InCarda, Merck, Novartis, and Roche Diagnostics. Drs Bergmark and Morrow are members of the TIMI (Thrombolysis in Myocardial Infarction) Study Group, which has received institutional grant support through the Brigham and Women's Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences.

## REFERENCES

1. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.
2. Stone GW, Sabik JF, Serruys PW, Kappetein AP. Everolimus-eluting stents or bypass surgery for left main coronary disease. *N Engl J Med*. 2017;376:1089.
3. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice M-C, Lembo N, Brown WM III, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med*. 2016;375:2223–2235.
4. Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, Trovik T, Kellerth T, Kalinauskas G, Mogensen LJH, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet*. 2020;395:191–199.
5. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IBA, Trovik T, Eskola M, Romppanen H, Kellerth T, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2016;388:2743–2752.
6. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
7. Bangalore S, Maron DJ, Stone GW, Hochman JS. Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and meta-analysis of randomized trials. *Circulation*. 2020;142:841–857.
8. Bainey KR, Alemayehu W, Welsh RC, Kumar A, King SB III, Kirtane A. Long-term clinical outcomes following revascularization in high-risk coronary anatomy patients with stable ischemic heart disease. *J Am Heart Assoc*. 2020;9:e018104. DOI: 10.1161/JAHA.120.018104.
9. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van` t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.
10. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816–2821.
11. Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II: subgroup with significant left main lesions. *Circulation*. 1976;54:III107–III117.
12. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563–570.
13. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.
14. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, et al. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol*. 2016;68:1233–1246.
15. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679.