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EDITORIAL COMMENT

# Revascularizing Diabetic Multivessel Coronary Artery Disease in the 2020s

## Forever Surgically Sweet?*

Rishi Puri, MBBS, PhD,[a] James M. Brophy, MD, PhD,[b] Michael J. Mack, MD[c]

In 2019, we witnessed the start of an intense debate of the merits of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) for treating significant left main coronary artery disease (CAD). Fueled by scrutiny from both their academic colleagues and the lay media, the EXCEL (Evaluation of XIENCE versus Coronary-Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial investigators are currently grappling with criticisms of their endpoint definitions and how these affected the recently published 5-year trial results (1). However, there is currently much less of a debate for the preferred revascularization strategy for patients with diabetes with multivessel CAD based on the outcomes of the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Diseases) trial and other studies (2–5).

The hallmarks of diabetic atherosclerosis are its diffuse, progressive nature that invariably couples with negative and/or constrictive coronary remodeling (6). PCI has been unable to favorably compare with CABG in optimizing medium- to long-term major adverse cardiovascular event rates in such patients, possibly because CABG more completely revascularizes the distal epicardial coronary bed, offering protection from upstream plaque events. In contrast, PCI provides local treatment, which is likely less effective in the setting of a more extensive and diffuse plaque burden.

Data from randomized controlled trials (RCTs) in which selected patients are studied under optimal, controlled conditions have consistently demonstrated superior outcomes with CABG compared with PCI in diabetic multivessel CAD (2,4,5). However, as with any randomized trial outcome data, the issue becomes the generalizability of the trial findings. Are the outcomes obtained within the confines of a trial environment translatable to the real world in which patient selection, operator proficiency, and patient care are more variable? Well-organized regional and/or national health care systems with meticulous data collection repositories provide the ability to retrospectively interrogate the breadth of evidence-based practice patterns that invariably affect a large population and may help answer that question.

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In this issue of the *Journal*, Tam et al. (7) attempted to address some knowledge gaps by systematically examining the short- and long-term follow-up in an unselected contemporary population-based cohort of patients with diabetes with multivessel CAD who underwent coronary revascularization (CABG or PCI) in Ontario, Canada. Although its observational design extends our knowledge of comparative revascularization outcomes across a

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From the [a]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; [b]Departments of Medicine and Epidemiology and Biostatistics, McGill University, Montréal, Quebec, Canada; and the [c]Baylor Scott & White Health, Dallas, Texas. Dr. Puri has received consulting fees from Medtronic, Amgen, and Cerenis; and holds minor equity in Centerline Biomedical. Dr. Brophy is supported by Les Fonds de Recherche Québec Santé. Dr. Mack has served as the co-principle investigator of the PARTNER trial (sponsored by Edwards LifeSciences) and of the COAPT trial (sponsored by Abbott); and has served as the study chair of the Apollo trial (sponsored by Medtronic).

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broader population of real-world patients, 2 main caveats warrant consideration: 1) the quality of data collected for administrative purposes; and 2) the uncertainty that patients who underwent PCI or CABG in this cohort were otherwise exchangeable beyond the treatment option they received.

The quality of the administrative data collected in Canada's universal health care system has been validated on multiple occasions (8) and is unlikely to represent any major concerns. Moreover, the overall quality of the interventions in this study, despite its all-comers population, was comparable to the excellent results obtained in the high-performance centers that participated in the FREEDOM trial, with 2-year CABG mortalities of approximately 7%, despite an on-average population that was 4 years older. Because clinical judgment, and not random allocation, was used in deciding which of these real-world patients were allocated to PCI versus CABG, the assumption of exchangeability almost certainly was not valid. In other words, there was almost certainly confounding by indication. However, all is not lost if exchangeability can be established by conditioning on a set of variables that predict the choice of treatment. This is the role of the propensity score—to calculate the probability of a given patient receiving a given treatment, and if patients in the 2 groups are matched to the same propensity score, then the choice of treatment may be seen as a pseudo-random allocation. However, it must be appreciated that although propensity scoring is extremely useful for the matching of measured confounders, there are no guarantees that other unmeasured confounders are equally distributed between the 2 groups. Therefore, unlike large randomized trials, there remains the possibility of residual confounding.

The E value (9) is a measure of the minimum strength of association, on the risk ratio scale, that an unmeasured confounder needs to have with both treatment and outcome to fully explain the observed specific treatment. It is an outcome association conditional on the measured covariates. A large E value implies that considerable unmeasured confounding would be needed to explain away an effect estimate, whereas a small E value suggests little unmeasured confounding would be needed to explain away an effect estimate. In the analysis of Tam et al. (7), for the composite 8-year freedom from major adverse cardiac and cerebrovascular events (hazard ratio: 2.00; 95% confidence interval: 1.86 to 2.14), E value calculations suggested the observed CABG benefit could be explained by an unmeasured confounder only if it was associated with both the treatment and the outcome by a relative risk of 3.13-fold each. This was above and beyond the measured confounders, but weaker unmeasured confounding would not do so. This suggests that the associations demonstrated by Tam et al. (7) were fairly robust for unmeasured confounding. Moreover, Tam et al. (7) demonstrated both skill and caution in the design and analysis of their study. At the design level, they carefully structured their follow-up time to avoid any notion of immortal time bias, and at the analytical level, they used state-of-the-art propensity score methods to minimize the omnipresent threat of confounding.

The analysis of Tam et al. (7) contributed useful evidence to further support CABG over PCI as the preferred technique for revascularizing patients with diabetes with multivessel CAD. Their results were not only compatible with the largest RCT to date (2) but were also consistent with a systematic review and Bayesian meta-analysis of 40 randomized trials that compared the 2 techniques (3). Their data appeared to extend the benefit of CABG (over PCI) to an unselected population of older adults with diabetes, and with a 4-fold large sample size than FREEDOM at 7 years, the study confirmed that the benefit of CABG was sustained out to 7 years.

The study by Tam et al. (7) provided substantial supporting evidence that, with all other things being equal, CABG is the preferred revascularization strategy in patients with diabetes with multivessel CAD, with strong evidence now emanating both in the clinical trial and real-world settings. Does that render CABG for multivessel diabetic CAD as the final treatment solution for now and foreseeable future? One could easily posit that based upon the totality of prevailing clinical evidence, that it is. However, we must remember that trial outcomes and their interpretation and relevancy change over time as other treatment options evolve. Let us not forget the role of guideline-directed medical therapy (GDMT) in altering the disease milieu. As background therapy, patients with diabetes and CAD should all receive high-intensity statins, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and perhaps PCSK9 inhibitors (10). If one were to subject a population with diabetes and multivessel CAD to contemporary state-of-the-art aggressive GDMT, how would that potentially change the results of the analysis by Tam et al. (7)?

Both interventional cardiology and cardiac surgical techniques have evolved. Do we need a new RCT in patients with diabetes and multivessel CAD that incorporates a heart team approach, a background of optimal GDMT, and routine assessment of invasive coronary physiology (iFR [instantaneous wave-free

ratio]/and fractional flow reserve), with subsequent intravascular ultrasound–guided PCI being used? Such a trial could incorporate the original SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial design of a RCT with companion registries of PCI and CABG for nonrandomizable patients as decided by the heart team (after all, this is arguably where the heart team really started), such that the evolving universe of disease management can be captured in its entirety (11). Best PCI practices, including the latest generation coronary stents with ubiquitous intravascular ultrasound guidance and coronary physiological assessment (as per the SYNTAX 2 study) (12), along with contemporary CTO (chronic total occlusion) techniques, could be used as well as the best surgical techniques, including multiple arterial grafting. Patients with diabetes and multivessel CAD who typically fare poorly with CABG are yet to be formally characterized. Therefore, the heart team discussion could pose the question when assessing such patients, "Who is not for CABG?" in deciding those patients who may still derive equivalent outcomes with state-of-the-art PCI (13).

In the interim, patient-centric shared decision-making via a heart team approach armed with the best evidence and practices should be the current standard. Clearly, there is not "one size that fits all" when treating such complex patients with diabetes and multivessel CAD. Winston Churchill once famously remarked: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning" (14). Perhaps the same can be said for the current state of play for revascularizing patients with diabetes and multivessel CAD.

**ADDRESS FOR CORRESPONDENCE:** Dr. Rishi Puri, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue (Mail Code J2-3), Cleveland, Ohio 44195. E-mail: purir@ccf.org. Twitter: @ClevelandClinic.

## REFERENCES

**1.** Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med 2019;381:1820–30.

**2.** Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.

**3.** Tu B, Rich B, Labos C, Brophy JM. Coronary revascularization in diabetic patients: a systematic review and Bayesian network meta-analysis. Ann Intern Med 2014;161:724–32.

**4.** The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217–25.

**5.** Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation 2001;104:533–8.

**6.** Puri R, Kataoka Y, Uno K, Nicholls SJ. The distinctive nature of atherosclerotic vascular disease in diabetes: pathophysiological and morphological insights. Curr Diab Rep 2012;12:280–5.

**7.** Tam DY, Dharma C, Rocha R, et al. Long-term survival after surgical or percutaneous revascularization in patients with diabetes and multivessel coronary disease. J Am Coll Cardiol 2020;76:1153–64.

**8.** Tu JV, Chu A, Donovan LR, et al. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART): using big data to measure and improve cardiovascular health and healthcare services. Circ Cardiovasc Qual Outcomes 2015;8:204–12.

**9.** VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-balue. Ann Intern Med 2017;167:268–74.

**10.** Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

**11.** Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.

**12.** Serruys PW, Kogame N, Katagiri Y, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15:e244–52.

**13.** Young MN, Kolte D, Cadigan ME, et al. Multidisciplinary heart team approach for complex coronary artery disease: single center clinical presentation. J Am Heart Assoc 2020;9:e014738.

**14.** Churchill W. The Lord Mayor's Luncheon, Mansion House, November 10, 1942. The Churchill Society London. Available at: http://www.churchill-society-london.org.uk/EndoBegn.html. Accessed July 1, 2020.

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