

EDITORIAL COMMENT

# CABG or PCI for Diabetic Patients With Left Ventricular Dysfunction

## Closing in on the Truth?\*

Eric J. Velazquez, MD,<sup>a</sup> Mark C. Petrie, MChB<sup>b</sup>



Coronary artery bypass grafting surgery (CABG) and percutaneous coronary intervention (PCI) have been in use for >50 and 40 years, respectively. Developed to relieve obstructive epicardial coronary artery disease (CAD) among patients with chronic stable angina, these revascularization procedures that have positively affected countless lives are increasingly applied to treat the emerging epidemic of patients with diabetes. In 2018, evidence from randomized controlled trials (RCTs) summarized in influential guidelines are used to support many revascularization decisions (relative to no revascularization and when choosing between CABG and PCI) among patients with chronic angina or acute coronary syndromes. Yet, the evidence is much thinner among the rapidly growing population of patients with left ventricular systolic dysfunction (LVSD) and, in particular, among diabetic patients. Remarkably, there have been no RCTs (or even sufficiently powered subgroup analyses of trials) completed that can direct decisions regarding CABG

or PCI among patients with diabetes, CAD, and LVSD. Against this background, the well-conducted observational study by Nagendran et al. (1) in this issue of the *Journal* is welcome and important.

SEE PAGE 819

Nagendran et al. (1) provide a comprehensive account of the outcomes of patients with diabetes and LVSD who were referred for diagnostic coronary angiography and who subsequently underwent CABG or PCI in the Province of Alberta, Canada between 2004 and 2016. Their analyses suggest that when faced with a diabetic patient with CAD and a left ventricular ejection fraction (LVEF) of  $\leq 35\%$  who is slated to undergo revascularization, the decision to proceed with CABG versus PCI is associated with a substantial 5-year reduction in major adverse cardiovascular events (29% vs. 61%;  $p < 0.001$ ) and mortality (19% vs. 35%;  $p = 0.002$ ). Similar statistical advantages favoring CABG over PCI were also observed in diabetic patients with better although still reduced LVEFs. Surprisingly, the benefit of CABG relative to PCI was not associated with either an early hazard or an excess rate of stroke; not surprisingly, CABG was associated with fewer repeat revascularization procedures. In summary, Nagendran et al. (1) provide evidence that the clinical decision to pursue a PCI revascularization strategy instead of CABG among diabetic patients with low LVEFs among patients in Alberta led to a >60% relative reduction and 16% absolute reduction in survival over 5 years. The public health impact of pursuing PCI or CABG in such patients is substantial, requires careful evaluation, and has few comparators in contemporary cardiovascular medicine. To put it in context, among patients with LVSD, the finding that sacubitril-valsartan reduced mortality rates compared with enalapril in

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the author and do not necessarily represent the views of JACC or the American College of Cardiology.

From the <sup>a</sup>Division of Cardiology, Department of Medicine, and Duke Clinical Research Institute, Duke University, Durham, North Carolina; and the <sup>b</sup>Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom. Dr. Velazquez has received research grants from the National Heart, Lung, and Blood Institute, Alnylam, Amgen, Novartis, and Pfizer; has provided consulting services for Abiomed, Amgen, Merck & Co., Novartis, Pfizer, and Philips Ultrasound, Inc.; and has received speakers bureau honoraria from Expert Exchange. Dr. Petrie has received speakers fees, research grants, or consulting honoraria from Takeda, Novartis, AstraZeneca, Maquet, Boehringer Ingelheim, Pfizer, Daiichi-Sankyo, Servier, Eli Lilly, and Novo Nordisk; and has served on clinical events committees for Roche, Bayer, Stealth Biotherapeutics, AstraZeneca, GlaxoSmithKline, Astellas, Cardiorentis, Reservlogix, and Boehringer Ingelheim.

patients with heart failure (HF) was associated with a 2.8% absolute reduction in mortality at a median of 27 months of follow-up led to swift changes in guidelines, and intense dissemination efforts are continuing (2). Will this report from Alberta lead to similar actions?

Likely not, but it should put the cardiovascular community on high alert and spur important next steps. Although observational registries can provide critical supporting information, especially regarding whether RCT findings can be generalizable to most patients, randomization is widely recognized as the only way to avoid confounding factors influencing findings and should remain the cornerstone of all practice-changing guidelines. This is particularly the case when investigating the pros and cons of revascularization because many issues, including procedural skill, prior experiences, and patient and family wishes, can influence both a clinician's choice and a patient's choice about whether to proceed to CABG or PCI or any revascularization procedure at all, thus leading to a highly selected study population.

Procedural risk calculators, albeit important leveling factors, are unlikely to alter engrained bias, favored clinical pathways, or even the best of intentions that drive a potential revascularization candidate to 1 approach or another. For example, the outcomes of all-comer diabetic patients with CAD with LVSD who may represent the majority of patients and never were referred for coronary angiography are not ascertained with the current study design. Even among the likely minority of patients with diabetes and LVSD who were referred to coronary angiography, 3,038 patients pursued medical therapy only (compared with the 2,837 who underwent subsequent revascularization). No information is provided on the gauntlet of commonly performed noninvasive studies or their findings that may have influenced the selection of candidates for CABG, PCI, or neither. Limited detail on the severity of cardiac dysfunction or HF or the duration or complications of diabetes in the patients included is provided. For example, what were the natriuretic peptide values or left ventricular (LV) volumes of these patients? Was the extent of mitral regurgitation or LV hypertrophy similarly distributed between PCI- and CABG-treated patients? Did CABG- and PCI-treated patients receive in similar proportions guideline-directed medical and device therapy for HF? Furthermore, details about the respective revascularization procedures and/or whether complete revascularization was achieved are absent. If a clinician identifies a patient as high risk for CABG—common among patients with LVSD—, she or he may divert that patient to PCI, possibly out of

mistaken beliefs that PCI and CABG provide similar relief of flow-limiting stenosis and that by avoiding an upfront surgical risk the overall benefit will be enhanced. As Nagendran et al. (1) correctly point out, valiant attempts at propensity matching cannot correct for all the variables that are factored into such decisions, and therefore their findings must be interpreted cautiously.

What did we know before the current study regarding the role of revascularization in patients with LVSD? The STICH (Surgical Treatment for Ischemic Heart Failure; [NCT00023595](#)) trial is the only trial to have randomized patients with an LVEF  $\leq 35\%$  (1,212 patients randomized to CABG and optimal medical therapy vs. optimal medical therapy alone) (3). After approximately 10 years of follow-up, CABG led to better long-term outcomes across the board, including an 8% absolute risk reduction in mortality corresponding to a median survival increase of nearly 18 months. Among those patients who were randomized, 40% had diabetes. In contrast to previous large trials of diabetic patients with an absence of LVSD (which showed greater benefit of CABG in those with diabetes), patients with diabetes compared with those without diabetes received a similar reduction in mortality from CABG in STICH (4). The challenge of managing patients with diabetes and LVSD who are undergoing CABG is emphasized by the diabetes subgroup analysis of STICH. Compared with patients without diabetes, those with diabetes spent more time on bypass and had more perioperative incident atrial fibrillation and renal failure.

Because it did not include a PCI arm, STICH cannot inform on the relative merits of CABG versus PCI, or indeed PCI versus medical therapy, in patients with LVSD with or without diabetes. Recently, a large meta-analysis evaluated the role of CABG, PCI, and medical therapy across randomized and observational studies of patients with LVSD albeit without evaluating diabetes separately (5). Similar to the Alberta experience, CABG was associated with improved survival when compared with PCI. Additionally, revascularization including with PCI was associated with improved survival compared with medical therapy alone. The only large, ongoing trial of PCI versus medical therapy in patients with LVSD is REVIVED (Safety and Efficacy of Percutaneous Coronary Intervention to Improve Survival in Heart Failure; [NCT01920048](#)), which has recruited approximately 370 of a projected sample size of 700 subjects in the United Kingdom. Although it is not a trial specifically of patients with diabetes, REVIVED is likely to include a fair number of patients with

diabetes and will likely report on this important subgroup.

Landmark trials of CABG versus PCI in patients with diabetes for the most part either excluded, or included very small numbers of, patients with LVSD or HF. The FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial demonstrated that patients with diabetes with generally preserved LV function derived a benefit from CABG compared with PCI but provided limited evidence regarding the relative benefits of each revascularization approach in patients with LVSD (having included only 3% of patients with an ejection fraction <40%) (6). Similarly, BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) included only 7% of subjects with LVSD (7). In the *Lancet* meta-analysis of 2009 of older RCTs of CABG against PCI, only 3% of subjects had HF, 17% had any abnormal LVEF, 16% had diabetes, and even fewer had the combination (8).

Studies of patients with diabetes and preserved LV function may have only limited relevance to patients with LVSD or HF. Let us consider CABG in patients with diabetes and LVSD compared with patients with good LV function. Although there are surprisingly few detailed observational studies that compare the structure and function of the hearts of diabetic patients with and without LVSD, it is likely that those with diabetes and LVSD have a more extensive range of adverse myocardial processes (prior myocardial infarctions large enough to cause LVSD, hibernating or nonviable myocardium, adverse remodeling, LV hypertrophy, and possibly glucose-related diabetic changes) than the myocardium of counterparts without LVSD. It is also likely that patients with diabetes and LVSD have smaller-caliber coronary arteries with more diffuse disease and more chronic total occlusions than counterparts without diabetes. Revascularization of such vessels, with either CABG or PCI, is a different prospect from revascularization of those less diseased vessels in patients with better LV function. Patients with diabetes and LVSD are likely to have a higher burden of comorbidities than those with diabetes without LVSD (although data documenting this are again surprisingly lacking). In STICH, patients with LVSD and diabetes had more baseline strokes and renal failure compared with patients with LVSD without diabetes. Vascular disease in patients with diabetes and LVSD also is likely to be more prevalent than in patients with diabetes without LVSD (aortic and subclavian disease are especially relevant), but this is also unstudied. All of

these factors and comorbidities are likely to affect the relative merits of CABG versus PCI.

What about the safety of PCI in patients with diabetes and LVSD? Periprocedural complications are likely to be greater in patients with diabetes with LVSD compared with those without LVSD. Limited cohorts report the frequency of complications, but vascular access is likely to be more challenging in patients with diabetes and LVSD. Other unknowns are periprocedural myocardial infarctions. Are these more frequent in patients with diabetes and LVSD (more stenting of complex, long lesions)? Are these periprocedural myocardial infarctions of greater prognostic significance than those in patients without LVSD? Nagendran et al. (1) report a higher rate of nonfatal myocardial infarctions among PCI-treated versus CABG-treated patients but does not provide information on mode of death, which would be informative. Are periprocedural strokes more frequent in patients with diabetes and LVSD or HF? It is very likely that periprocedural mortality rates are also greater if PCI is performed in patients with diabetes and LVSD or HF. Anemia and bleeding may be more common in patients with diabetes with LVSD compared with those without LVSD. Additional unknowns of PCI in diabetes and LVSD include rates of incomplete revascularization, stent thrombosis, and in-stent restenosis.

To date, studies of PCI versus CABG in patients with LVSD or HF have rested in no man's land among the trenches of cardiac surgeons, interventional cardiologists, and cardiologists who treat HF, the STICH trial being a notable exception. Most cardiac surgery studies preferentially enroll patients with good LV function, whereas cardiologists who treat HF have mostly performed trials of pharmacological approaches and cardiac resynchronization therapy. The interventional cardiology community has conducted a multitude of trials of stents and adjunctive therapies but have performed few trials in (or including) patients with LVSD and/or HF. Nonetheless, hope is on the horizon because the development of new devices and procedures has required increasing collaboration among these specialties. An array of structural therapies for HF (e.g., MitraClip [Abbott Vascular, Lake Bluff, Illinois], inter-atrial septal devices, percutaneous LV volume reduction therapy) has brought these specialists together. Equally relevant are the advances in coronary intervention (the advent of complex high-risk and indicated PCI [CHIP]) that has resulted in necessary collaboration between interventional cardiologists and cardiologists who treat HF. In particular, therapies such

as Impella (Abiomed, Danvers, Massachusetts) and extracorporeal membrane oxygenation require multidisciplinary focus on the patient with LVSD and HF.

From this perspective, the challenge of altering practice standards for patients with diabetes, CAD, and LVSD through the conduct of RCTs may seem at worst Sisyphean and at best nearly impossible. Thankfully, the Alberta study by Nagendran et al. (1) not only highlights the value of carefully collected registry data to inform best practices when RCTs are just not available but also points to the future when such RCT data should be increasingly available. Appropriately, there is increasing enthusiasm regarding the use of coordinated electronic health data repositories akin to what Nagendran et al. (1) used to track the complexity of care and critical outcomes across health systems, provinces,

states, or countries. Now imagine pragmatic RCT protocols of PCI versus CABG for LVSD embedded within this larger data landscape, and one can envision a day soon when patients and clinicians will be neither surprised nor, worse, disappointed regarding the decisions made in routine care. Until then, these findings in support of CABG should be carefully integrated into discussions with diabetic patients with LVSD who are facing revascularization.

---

**ADDRESS FOR CORRESPONDENCE:** Dr. Eric J. Velazquez, Cardiovascular Imaging Section, Cardiac Diagnostic Unit and Echocardiography Laboratories, Duke University Health System, DCRI Clinical Trials, Duke Clinical Research Institute, 2400 Pratt Street, DUMC Box 3850, Durham, North Carolina 27705. E-mail: [eric.velazquez@dm.duke.edu](mailto:eric.velazquez@dm.duke.edu).

---

## REFERENCES

1. Nagendran J, Bozso SJ, Norris CM, et al. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. *J Am Coll Cardiol* 2018;71:819-27.
2. McMurray JJ, Packer M, Desai AS, et al., PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
3. Velazquez EJ, Lee KL, Jones RH, et al., STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;374:1511-20.
4. MacDonald MR, She L, Doenst T, et al. Clinical characteristics and outcomes of patients with and without diabetes in the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *Eur J Heart Fail* 2015;17:725-34.
5. Wolff G, Dimitroulis D, Andreotti F, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail* 2017;10:e003255.
6. Farkouh ME, Domanski M, Sleeper LA, et al., FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84.
7. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-15.
8. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;373:1190-7.

---

**KEY WORDS** diabetes mellitus, ischemic cardiomyopathy, revascularization