The “Fragility” of Mortality Benefit of Coronary Artery Bypass Graft Surgery in Diabetics*

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The relative merits of guideline-directed medical therapy (GDMT), percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG) for the management of stable ischemic heart disease is still hotly debated, despite more than 3 decades of clinical trials. Fundamental to this debate are the data that although myocardial infarction (MI) can result from lesions that are flow-limiting, lesions that are non-flow-limiting, which greatly outnumber the flow-limiting lesions, contribute to a good proportion of future MI (68% by lesion stenosis <50%) (1). As such, strategies that target only the flow-limiting lesions (such as PCI alone without GDMT) are theoretically inferior. GDMT targets both flow-limiting and non-flow-limiting (but potentially vulnerable) lesions (Figure 1). However, GDMT is heavily dependent on patients’ medication compliance, and has the limitation of side effects. CABG targets the flow-limiting lesions as well as some non-flow-limiting lesions (in the 50-mm segment of the coronary artery that is bypassed) (Figure 1). However, CABG is invasive and is associated with upfront morbidity and mortality with a prolonged recovery time. PCI targets only the flow-limiting lesions but has the advantage of being less invasive than CABG, with lower upfront morbidity and mortality, and shorter recovery time.

Patients with diabetes mellitus have a greater burden of atherosclerotic cardiovascular disease with high morbidity, mortality, and health care utilization, and as such, optimal management of such patients is of paramount importance. The landmark FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (2) randomized 1,900 patients with diabetes (83% with 3-vessel disease) to either CABG or PCI (using the first-generation drug-eluting stents [DES]) and showed a significant benefit of CABG at reducing the composite outcome of death, MI, or stroke at a median follow-up of 3.8 years, driven by a decrease in MI (p < 0.001) and death (p = 0.049), but increase in stroke (p = 0.03). The FREEDOM Follow-On trial published in this issue of the Journal provides further insights into the durability of the results over extended follow-up (3). Over a median follow-up of 7.5 years, CABG was associated with a significant reduction in death when compared with PCI (18.3% vs. 24.3%; p = 0.01) in the overall randomized cohort, a reduction of 6 percentage points, or a relative decrease of 24.7%. These data let us calculate a number needed to treat (for mortality at 7.5 years of follow-up) of 21 (95% confidence interval: 12 to 58), a number needed to harm (for stroke at 3.8 years of follow-up) of 56 (95% confidence interval: 30 to 363) and a likelihood to be helped or harmed (likelihood to be helped = number needed to harm/number needed to treat) ratio of 2.7 for CABG over PCI, supporting current recommendations by national and international guideline committees to consider CABG over PCI in patients with diabetes and multivessel disease (4,5).

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CABG in the FREEDOM trial. Data from the FREEDOM Follow-On trial lets us calculate a “fragility index” of 16, suggesting that 16 more deaths in the CABG group will render the results to be statistically nonsignificant (p $\leq 0.05$). The fragility index of 16 is nontrivial given that the loss to follow-up (>50% of the original cohort was not followed up long term) is far greater than this number. In addition, in the cohort with extended follow-up, the difference in mortality did not reach statistical significance (p = 0.08), although the trend favored CABG.

A savvy practitioner may want to know the robustness (or fragility) of the mortality benefit of CABG in patients with diabetes given the ever-evolving medical therapies. The BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial compared prompt revascularization (stratified by PCI or CABG) with intensive medical therapy or intensive medical therapy alone in 2,368 patients with diabetes. In the CABG stratum (n = 763, 53% with 3-vessel disease) of the trial, there was no difference in mortality between CABG and medical therapy (p = 0.33) at 5-year follow up (6).

Thus, whereas CABG was no better than medical therapy in the BARI-2D trial, it was superior to PCI in the FREEDOM trial for mortality at 5-year follow-up. Of note, neither the FREEDOM trial nor the CABG stratum of the BARI-2D trial was adequately powered to show a mortality difference at 5 years. The seemingly discordant results are either due to enrollment of patients with more extensive coronary artery disease (CAD) in the FREEDOM trial who potentially benefited from CABG or due to more stent-related events in the PCI group with the use of first-generation DES (discussed later in the text).

GDMT has evolved since the BARI-2D and FREEDOM trials with therapies proven to reduce death and/or MI. Novel oral hypoglycemic agents such as sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce death and non-fatal MI (7), and glucagon-like peptide (GLP)-1 receptor agonists reduce death in patients with diabetes (8). Similarly, therapies not used in the FREEDOM trial such as the proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors reduce nonfatal MI (9), low-dose rivaroxaban (with aspirin) reduces death (10), and canakinumab, a monoclonal
antibody targeting interleukin-1β, reduces MI (11). The ongoing ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) (12) and ISCHEMIA-CKD (ISCHEMIA-Chronic Kidney Disease) trials (13) have enrolled a good proportion of patients with diabetes (majority with multivessel CAD) and will provide insights into the outcomes with invasive strategy (cardiac catheterization with PCI or CABG if feasible, with optimal medical therapy) or conservative strategy (optimal medical therapy alone) in patients with stable ischemic heart disease.

A savvy interventionalist may want to know the robustness (or fragility) of the mortality benefit of CABG over PCI in patients with diabetes given the improvement in stent technology and PCI techniques (fractional flow reserve use and chronic total occlusion success rates). The naysayers will opine that improvement in stent technology will not have an impact on the outcomes of death or MI. However, data from clinical trials, meta-analysis of clinical trials, and registries consistently show reduction in death and/or MI (driven by decreases in stent thrombosis and restenosis) with newer-generation DES when compared with early-generation DES or bare-metal stents (14,15). More recent data seem to suggest further reduction in MI with the use of ultra-thin-strut DES when compared with current thin-strut second-generation DES (16). Can improvement in stent design narrow the mortality gap between CABG and PCI? In a network meta-analysis of clinical trials, although a mortality benefit of CABG was observed when compared with PCI using first-generation DES in patients with diabetes, the mortality gap narrowed to statistical nonsignificance when the comparator was newer-generation DES (17). Similarly, in an analysis of over 16,000 patients with diabetes and multivessel CAD from the New York State registries, PCI with second-generation DES was associated with lower upfront risk of death and stroke when compared with CABG. At long-term follow-up, there was no significant mortality difference between PCI and CABG (18). Similarly, in a meta-analysis of the only 3 randomized controlled trials of CABG versus PCI using newer-generation DES, major adverse cardiovascular event was lower with PCI when compared with CABG at 30 days. Over long-term follow-up (3 to 5 years), there was no difference in outcomes between the 2 groups, and the diabetes status was not an effect modifier in this analysis (19). Some may also argue that improvement in PCI techniques such as fractional flow reserve-guided PCI and increased success rate with chronic total occlusions may further bridge the gap between PCI and CABG. However, these strategies have not proven to reduce death in randomized trials, although they improve the rates of complete (or functionally complete) revascularization.

Finally, a savvy cardiac surgeon may be rightly frustrated over lack of practice change despite compelling evidence for CABG in patients with diabetes (20). Given that PCI is performed predominantly at the time of diagnostic coronary angiography, even a savvy patient may be deprived of the benefit of consulting with a surgeon at a time when long-term outcomes are at stake. Patients are presumably diagnosed with diabetes before the coronary angiography, and a discussion indicating survival benefit with CABG should be initiated in advance of the diagnostic procedure, in order to allow enough time for the patient and family members to digest the information and make a decision that fits the individual preferences and lifestyle needs. Furthermore, recent advances favor CABG using multiple arterial conduits (e.g., left internal thoracic and radial artery) even in diabetic patients; this modern approach is associated with improved outcomes compared with the more traditional single internal thoracic artery and vein combination that was predominantly practiced in the FREEDOM trial (21).

Despite this, it is foolish to ignore the results from the FREEDOM and FREEDOM Follow-On trials (3). Equally foolish is to ignore the wealth of data supporting clear impact on death and/or MI with improvements in medical therapies and stent technology. Whether a BARI-2D-guided approach or an “ISCHEMIA”-guided approach or a “FREEDOM” trial-guided approach is considered, the optimal management of patients with diabetes and multivessel disease should be individualized using a heart team to weigh the upfront risk of CABG with potential late benefits, ability to completely revascularize with PCI, ability of patient to be compliant with medication therapies, and most importantly, patient preference.

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