The SYNTAX score according to diabetic status: What does it mean for the patient requiring myocardial revascularization?

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Feature Editor's Note—*Selecting the optimal strategy for revascularization, that is, percutaneous coronary intervention (PCI) versus surgical coronary artery bypass grafting (CABG), for individual patients is a complex process guided by many clinical characteristics and features. Since its original description, the synergy between PCI with a TAXUS (Boston Scientific, Marlborough, Mass) drug-eluting stent and cardiac surgery (SYNTAX) score has been incorporated into the decision process of many heart teams to provide an evidence-based decision process for patients presenting for consideration for revascularization for coronary artery disease. The SYNTAX score characterizes the extent of coronary disease in terms of the number of lesions, their functional importance, and their complexity. Previous studies have categorized the SYNTAX score to identify patients at low (≤ 22), medium (23-32), and high (≥ 33) risk and demonstrated superior outcomes for patients receiving CABG over PCI, primarily in those patients with high SYNTAX scores. Recent data from the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) study and the FREEDOM Follow-On study call into question the value of the SYNTAX score as a factor in determining revascularization strategy in patients with multivessel coronary disease and diabetes mellitus. Data from these trials confirm the benefit of CABG in this patient population independent of the SYNTAX score. In this issue of the Journal, Ruel and colleagues provide an insightful editorial of the importance of the observations from the FREEDOM and FREEDOM Follow-On study and how these observations should influence current strategies for coronary revascularization.*

In a recent article published in the *Journal of the American College of Cardiology*, Esper and colleagues¹ reported that in 1900 patients with diabetes and multivessel coronary artery disease (CAD) randomized to percutaneous

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Central Message

We appraise the latest research from the FREEDOM trial and other studies that compared PCI with CABG. The future is brighter for CABG, but we must work together to improve this important operation.

The Invited Expert Opinion provides a perspective on this topic based on the following paper: *J Am Coll Cardiol.* 2018;72:2826-37. <https://doi.org/10.1016/j.jacc.2018.09.046>.

See Commentary on page 861.

coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, there was no significant interaction (ie, variation in outcome) between the benefit of having undergone CABG and a patient's SYNTAX score (SS) at trial enrollment. Overall, patients who received CABG experienced approximately one-third less major adverse cardiac and cerebrovascular events, regardless of whether their SS was low (≤ 22 ; in 35.4% of patients), intermediate (23-32; 44.8% of patients), or high (≥ 33 ; 19.9% of patients).¹ The cumulative incidence of major adverse cardiac and cerebrovascular events at 5 years ranged between 37% (low SYNTAX score) and 44% (high SYNTAX) in the PCI group versus 26% (low SYNTAX) and 30% (high SYNTAX) in the CABG group.

In other words, these data indicate that CABG should preferentially be used over PCI in any diabetic patient with multivessel CAD who has a significant survival potential, regardless of the SS and unless contraindications to CABG exist... that is, even if the SS is low or intermediate.

Two aspects of the study by Esper and colleagues¹ are striking. First, the FREEDOM trial enrolled exclusively patients with diabetes and multivessel CAD (only 8 patients

had significant left main disease), of whom 17% had 2-vessel CAD.² Consequently, the study provides the most definitive information regarding the choice of revascularization in diabetic patients with at least moderate CAD severity. Second, the FREEDOM trial also used the concept of hard cardiovascular events (HCEs), defined as the composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke. Although the acronym HCE was coined only for this post hoc analysis, its end point components were used in the original study protocol and main analysis of the trial.² This HCE end point does not include the sometimes disregarded event of target vessel revascularization, which disfavors PCI and is considered by some to represent a softer cardiovascular end point than stroke or myocardial infarction (Table 1). Nevertheless, despite the exclusion of target vessel revascularization in FREEDOM, HCEs occurred 42% more frequently with PCI than with CABG at 3.8 years of follow-up ($P = .005$). There was also a 50% excess in all-cause mortality in the PCI over the CABG group ($P = .049$).

Recently, another related publication, the FREEDOM Follow-On study, confirmed these findings over a follow-up period extended to twice that of the original FREEDOM trial cohort. Patients were followed, in a proportion of approximately one-half because of funding constraints, for a median duration of 7.5 years. Over that extended follow-up, Farkouh and colleagues³ found a 36% excess mortality with PCI over CABG ($P = .01$), again with no significant interaction according to SS or whether patients had presented with 2-vessel versus 3-vessel CAD. Overall, the major cardiac adverse events rate in the FREEDOM trial was higher after PCI than CABG for every tercile of SS, indicating that the SS did not identify a population of diabetic patients with multivessel disease for whom PCI may be equivalent or superior to CABG.

FREEDOM AND THE SYNTAX SCORE IN CONTEXT

Myocardial revascularization research comparing PCI and CABG has evolved considerably over the last decade. This has resulted in part from the massive influx of funding, often by stent makers, for large and expensive trials such as SYNTAX, NOBLE, and EXCEL, each of which enrolled more than 1000 patients to compare PCI and CABG in a head-to-head fashion. Although FREEDOM was funded by the National Institutes of Health and led by noninterventional cardiologists, it too received funding from stent makers. In the trials landscape, FREEDOM is tied with EXCEL (which at $N = 1905$ enrolled 5 patients more) as the largest modern trial of PCI versus CABG; however, FREEDOM was a superiority trial, has a longer follow-up, and captured more events than EXCEL. It should be noted that a noninferiority trial design,

TABLE 1. Leveraging factors in the design and methodology of myocardial revascularization trials that compared percutaneous coronary intervention and coronary artery bypass grafting

Factors that favor PCI	Factors that favor CABG
Careful selection of patients based on PCI-favorable anatomic characteristics, including isolated left main CAD	Inclusion of patients who are generally at low surgical risk
Short-term follow-up	Lack of an early functional end point, such as pain, mobility, transfusion, rehospitalization
Low incidence of diabetes	High incidence of multivessel CAD
Very low incidence of patients with left ventricular dysfunction	
Composite and optimized end point definitions (eg, periprocedural myocardial infarction; ischemia-driven target vessel revascularization)	Endpoints that include target vessel revascularization
PCI cases generally receiving better guidelines-directed medical therapy ¹⁵	
Trial funding and assistance by stent maker or catheterization laboratory supplier	
Noninferiority trial design with optimized noninferiority margin	
Subgroups analyses that are underpowered or not supported by a statistically significant test for interaction	
Expertise bias (expert PCI centers vs regular CABG centers)	

For details, see Ruel and colleagues.¹⁷ PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease.

as was used in SYNTAX and EXCEL, and a funding source originating from industry, which took place in all of the stated trials, are each associated with an odds ratio of approximately 3 toward a trial's results being favorable to the sponsor.⁴ Other methodological considerations enabling the possible equivalence of PCI to CABG include the use of shorter follow-up end points and the performance of subgroup analyses that are both underpowered and not supported by a significant test for interaction. In this regard, subgroup analyses can provide forest plots that appear non-different among key patient subgroups, but merely as a result of type II error.^{5,6} This way, several claims that PCI may be as good as CABG for specific subgroups of patients (eg, those with isolated left main CAD that, once separated from all trial patients, lead to reduced statistical power) have made their way even to high-profile publications.^{5,7}

AN APPROXIMATELY 40% OUTCOME BENEFIT WITH CORONARY ARTERY BYPASS GRAFTING OVER PERCUTANEOUS CORONARY INTERVENTION

The results of FREEDOM and its secondary analyses are not surprising and have been corroborated by meta-analyses of diabetic patients undergoing revascularization, in which it was also notable that newer stent technology did not improve the often seen approximately 40% benefit on hard outcomes obtained from use of CABG over PCI.⁸ The 4-year results of the EXCEL trial were presented at the Transcatheter Cardiovascular Therapeutics meeting in the fall of 2018 and revealed a statistically significant mortality excess, also by approximately 40%, in the PCI versus the CABG group.⁹ We consider that the overarching finding that arises from recent trials comparing PCI and CABG is that despite decades of industry-funded, noninferiority trials involving shorter follow-up, we now have renewed evidence that CABG is superior to PCI for most patients with advanced CAD with, as a consequence, an increase in CABG numbers noted worldwide.

WHY IS CORONARY ARTERY BYPASS GRAFTING MORE EFFECTIVE?

CABG, provided that it can be performed with very low risk, represents a different type of revascularization than PCI. By providing a de novo coronary artery segment to each bypassed lesion, CABG enables 3 mechanistic effects: (1) *perfusion of the grafted coronary axis*, in a way similar to PCI but with the added benefit of distal protection against the development of new proximal and mid-vessel lesions; (2) an *endothelial function* effect, by adding nitric oxide-producing arterial segments that may curtail against native disease progression, especially with arterial grafts and in contrast to PCI, which can exacerbate CAD through mechanisms that include endothelial dysfunction and chronic inflammation^{10,11}; and (3) a newly perfused *distal bed for collateralization*.¹² Furthermore, the implications of a failed CABG graft, provided that it was performed safely and meticulously, are considerably less than those of a failed stent, which has high mortality and morbidity from direct compromise of the coronary axis.¹³ The loss of a CABG graft is in most cases indolent and returns the subtended myocardial segment to unsupplemented perfusion (provided that the distal anastomosis was flawlessly constructed, retrogradely and antegradely) and subjected to guideline-directed medical therapy.¹⁴

THE FUTURE OF CORONARY ARTERY BYPASS GRAFTING: SAFER, BETTER, AND LESS INVASIVE

CABG still is likely underused. As such, if cardiac surgeons are to take part in heart team discussions at their

institution and advocate for the appropriate treatment of patients with CAD who require revascularization, 2 points are germane. First, surgeons should know the indications for CABG thoroughly and understand their genesis, as well as the strengths and pitfalls of the studies, several of them recent, that have attempted to claim noninferiority of PCI over CABG in patients with advanced CAD. For a comprehensive reference, the reader is encouraged to consult the latest Myocardial Revascularization Guidelines,¹⁶ as well as a recent article appraising the trials and pooled analyses that have contributed to these guidelines.¹⁷ Second, it is important for surgeons to work at improving the techniques and outcomes of CABG in the same way that relentless efforts have been made to improve PCI for the benefit of patients with CAD worldwide.

The cardiovascular community often hears that stents are “getting better,” but CABG surgery is getting better too, with less strokes in the contemporary era than during SYNTAX and FREEDOM¹⁸; better outcomes with use of the radial artery as a second arterial graft¹⁹; and better adherence to secondary prevention in patients undergoing CABG.²⁰ Nevertheless, we have to collectively strive to make CABG even safer, better, and less invasive. A resurgence in CABG signifies a unique and likely last opportunity to improve this operation for the sake of our future patients. Three areas should be focused on: (1) CABG must be made extremely safe, from a mortality and morbidity point of view, including stroke; (2) the long-term outcomes of CABG must be optimized by the use of multiple arterial grafts and guideline-directed medical therapy, so that the operation can become curative rather than merely palliative; and (3) CABG must be made less invasive, because approximately 30% of patients undergoing CABG still report pain 1 year after sternotomy,²¹ and only 24% may have sternal union by 6 months after surgery.²² The latter also is supported by quality of life data indicating that full recovery from CABG takes at least 6 months.^{23,24}

CONCLUSIONS

In the research arena, although no new, large PCI versus CABG head-to-head trial is in the works, the FAME 3 study is ongoing, and another large-scale trial is being designed to evaluate PCI versus CABG in patients with systolic left ventricular dysfunction. It is essential that inferential imbalances from the past are not perpetrated and that cardiac surgeons assume a genuine co-leadership role in each of those trials. After 50 years of existence, CABG remains one of the cardiac surgical procedures that serves our patients the best, having resulted in countless lives saved and improved. It is now time to regroup as a strong cardiovascular community to optimize this potentially curative operation and all the ancillary care around it, in order to make CABG as safe and effective as possible, so that

future patients with advanced CAD can reasonably hope to be cured from their ailment.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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