Editorial

Diabetic Heart Disease and Interventional Cardiology: How Can Clinical Outcomes Be Improved? Revascularization Guided by Hemodynamic Parameters (Fractional Flow Reserve)

Cardiopatía diabética y cardiología intervencionista: ¿cómo se puede mejorar los resultados clínicos? Revascularización guiada por parámetros hemodinámicos (reserva de flujo fraccional)

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Diabetes mellitus (DM) is an increasingly common disease, with an estimated prevalence of greater than 15% worldwide. Patients suffering from DM experience an increased risk of coronary heart disease, with a concomitant raise in cardiovascular morbidity and mortality. Accordingly, these patients represent 20%-30% of those undergoing revascularization procedures worldwide. Advances in the safety and technical success of percutaneous coronary intervention (PCI), along with preferences for less invasive methods have catalyzed a significant increase in PCI among patients with DM. However, DM represents a complex milieu for management of coronary heart disease, with known physiological effects including endothelial dysfunction, a prothrombotic state, and an increased pace of atherosclerotic plaque development. These features, and DM itself, confer an augmented risk of adverse cardiovascular outcomes.

Multivessel disease is common among diabetic subjects with coronary artery disease, and leads to the consideration of an optimal revascularization strategy. Few studies have investigated the difference in outcomes between PCI and coronary artery bypass grafting (CABG) specifically in patients with DM. To date, the largest trial devoted to studying revascularization in patients with DM and multivessel disease is the FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease); it is a randomized-controlled trial that compares the outcomes of PCI versus CABG in patients with DM and multivessel disease. In this trial, patients with DM requiring revascularization with angiographically proven multivessel disease, and lesions amenable to either PCI or CABG were randomized to complete coronary revascularization using 1 of these techniques. The primary outcome (all cause mortality, nonfatal myocardial infarction [MI], and nonfatal stroke) at 5 years was more common among patients treated with PCI than with those treated with CABG (26.6% vs 18.7%, P=.005). Among individual components of the primary outcome, there was a significantly increased long-term risk of all cause mortality and nonfatal MI with PCI as compared to CABG. CABG, however, was associated with an increased risk of nonfatal stroke. The severity of strokes in the CABG group was also found to be twice as likely to severely disable the patient as compared to strokes occurring in the PCI group.

The FREEDOM trial largely validates smaller studies, subgroup analysis, and meta-analysis attempting to compare methods of revascularization in diabetic patients with multivessel disease. The CARI Dia (Coronary Artery Revascularization in Diabetes trial) randomized trial comparing PCI to CABG, while smaller in size, was also dedicated to patients with diabetes, with a significant fraction of the diabetics suffering from multivessel disease. Although this study was terminated early due to lack of funding, it showed no significant difference in 1-year mortality. Like the FREEDOM trial, however, it revealed an increased risk of stroke in the CABG group. Concomitantly, while a majority of patients were treated with drug-eluting stents (DES) in this trial, there was a significantly increased need for repeat revascularization procedures with PCI. The SYNTAX trial (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) randomized 1800 patients with multivessel or left main disease (1709 of these patients had multivessel disease) to PCI with DES versus CABG, and 30% of enrolled subjects had DM. In the SYNTAX trial, complete revascularization was the goal for both study groups, and the average number of treated vessels and stents among patients with PCI for left main disease or multivessel disease was 3.6 lesions and 4.6 stents, respectively. One-year outcomes were not different between the PCI and CABG study groups for all cause mortality or MI. However, there were significantly higher rates of major adverse cardiovascular events and cerebrovascular events with PCI, mainly attributable to the significantly higher rates of target lesion revascularization in the PCI group. Three-year outcomes were similar to these findings, with no significant difference in all cause mortality and a persistently elevated rate of target lesion revascularization associated with PCI. Subgroup analyses of subjects with DM revealed no difference in a combined outcome of all cause mortality, nonfatal MI, or nonfatal stroke at 3 years, but did demonstrate a significantly higher risk of repeat
revascularization with PCI as compared to CABG.\textsuperscript{5} These findings were dependent on the SYNTAX score—an angiographic grading system to quantify PCI complexity. With low SYNTAX scores (<22), there were no significant differences in the primary outcome, but with high SYNTAX scores (>33), major adverse cardiovascular event rates and cerebrovascular event rates were lower, regardless of DM status.

Similar results, showing late survival benefit related to CABG in subjects with multivessel disease, were found in a nonprotocol specified subgroup analysis of the BARI (Bypass Angioplasty Revascularization Investigation) trial, a landmark attempt to compare revascularization using either CABG or plain old balloon angioplasty. Of the >1800 randomized patients, roughly 20% were diabetic, and 40% had 3-vessel disease. Only patients who were likely to obtain complete revascularization from either CABG or PCI were randomized. Ten-year outcomes in patients with DM revealed a statistically significant survival benefit with CABG as compared to plain old balloon angioplasty\textsuperscript{6}; postulated to be related to the prevention of fatalities resulting from spontaneous plaque rupture and MI. BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes Randomized Trial) was a 2 × 2 factorial randomized trial, designed to compare revascularization with optimal medical therapy to revascularization alone in patients with type 2 DM as the primary analysis.\textsuperscript{7} Subjects were stratified by the preferred mode of revascularization: CABG or PCI. The CABG stratum showed a greater mortality benefit in the revascularization group as compared to the medical therapy group, unlike the PCI stratum. Whether this was due to an increased extent of disease in those considered for CABG or whether there was a treatment benefit for CABG over PCI could not be determined from this study because of the lack of randomization between the 2 modes of revascularization.

A meta-analysis of 10 early clinical trials was performed to evaluate PCI versus CABG in patients with DM.\textsuperscript{8} The collective analyses of several landmark trials revealed a substantially lower risk of mortality associated with CABG in patients with DM. It is important to note that the majority of these studies utilized angioplasty only, as they were conducted before the use of stents or DES; however, the objective of complete revascularization with either PCI or CABG was similar to contemporary studies of PCI versus CABG.

While these results offer guidance towards treatment selection; treatment approaches used for PCI and CABG in all these studies have essentially focused on the strategy of complete revascularization. Until the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial was reported, there were no randomized trials that defined complete revascularization as an ideal treatment strategy for either CABG or PCI. Data supporting complete revascularization of all angiographic lesions during multivessel disease treatment with PCI or CABG has been observational (nonrandomized); it is thus limited by the selection bias of patients in whom full revascularization is feasible and in whom there is also a lower risk of procedural and future adverse events. The concept of targeted treatment of vessels with physiologically significant stenosis and not just angiographically significant stenosis may allow improved outcomes for multivessel disease patients who are treated with either PCI or CABG.

The technique of fractional flow reserve (FFR) utilizes the placement of a pressure wire across a potentially significant lesion, and under conditions of maximal coronary blood flow, measures the ratio of the pressure distal to versus the pressure prior to a lesion or series of sequential lesions within a given artery. As compared to traditional angiography, which can only provide an anatomic evaluation, FFR provides a functional assessment of the presence of flow reduction, which has been shown to correlate well with ischemia as detected by nuclear scintigraphy. The FAME trial sought to evaluate the clinical utility of FFR by comparing angiography versus FFR guidance for lesion selection during DES PCI in over 1000 patients, 25% of whom had DM.\textsuperscript{9} Only lesions with FFR<0.8 were considered to warrant PCI in the FFR arm. FFR guidance resulted in fewer overall stented lesions and a 2-year analysis revealed significantly reduced mortality and MI with the use of FFR relative to pure angiographic guidance, not just corroborating the simple physiologic benefit of FFR, but also the morbidity and mortality advantages of stenting across physiologically relevant lesions.

The recent FAME2 trial (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2), evaluated the use of FFR to guide therapy in patients with stable coronary artery disease in order to prevent future urgent revascularizations.\textsuperscript{10} Lesions determined to have FFR<0.8, were randomized to either revascularization with DES or the best available medical therapy. Recruitment was halted prematurely based on a higher rate of the primary endpoint of death, MI, or urgent revascularization in the medically treated group, driven mainly by revascularization. Due to the premature termination of enrollment due to differences in outcome, long-term survival analyses are not available for the patients in the FAME2 trial,\textsuperscript{10} but would be invaluable in the assessment of need for revascularization in stable coronary disease. Nevertheless, the FAME2 trial stirs up interest in the hypothesis that choosing stable, yet physiologically relevant lesions could be associated with a reduction in acute presentations for revascularization, some of which were associated with acute coronary syndromes in this trial. Further, the design of the trial, using FFR guidance rather than angiography-guided complete revascularization, stands in contrast with other trials that compared medical therapy to PCI with medical therapy, such as the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).\textsuperscript{11}

There have been smaller studies investigating the use of FFR to guide surgical revascularization. A study of 168 eligible patients planned for CABG was performed, wherein all patients had FFR measurements prior to surgery.\textsuperscript{12} At 1-year analysis, treated lesions with initial FFR<0.75 had a lower incidence of graft occlusion as compared to nonsignificant lesions.

Analysed together, these data suggest that FFR certainly is advantageous in lesion selection for PCI, and additional studies among patients undergoing CABG are warranted. To date, however, there have been no major trials investigating the use of FFR to guide clinical decision making in patients with DM.

Further complexity exists, as PCI and CABG are fundamentally different therapeutic approaches to the same problem. PCI, with its origins in plain old balloon angioplasty, is a focal solution, and was not designed to address morbidity related to the development of de novo plaques. Advances in PCI over the last decade have revolved around optimizing acute success rates and minimizing restenosis, both local phenomena. On the other hand, CABG is a regional therapy that has shown benefit over local therapies in zones at high risk for acute thrombosis with local therapies.\textsuperscript{13} DES has benefitted DM patients by substantially reducing restenosis and the need for repeat procedures within the stented lesion, which has been a particular problem for diabetics treated with bare metal stents.\textsuperscript{14} The improved safety and durability of treating more complex lesions has paved the way for interventional cardiologists to achieve more complete revascularization.

The strategy of FFR guidance for PCI may have its most significant impact on these local factors, by avoiding complications of restenosis related to treating angiographically but not physiologically significant lesions during PCI, and avoiding the problems of native vessel accelerated plaque progression or saphenous vein graft degeneration during CABG. Using FFR guidance may improve
outcomes among diabetic multivessel disease patients treated with PCI.

Whether, such a strategy could narrow the gap in long-term survival between diabetic treated with PCI versus CABG is, however, an open question that depends on the impact of these procedures on the progression of atherosclerosis and the potential protection that each revascularization strategy offers from clinical manifestations of new plaque rupture.

The question that remains is: can a previously targeted therapy be used throughout the coronary vasculature so as to prevent unstable plaque rupture, particularly among DM patients who have a higher than average risk of disease progression and spontaneous plaque rupture? The width of the gap between revascularization strategies may also depend on how completely medical therapy can reduce the overall risk of plaque rupture. Medical treatments that have been demonstrated to reduce the risk of future plaque rupture (antiplatelet agents, HMG-CoA reductase inhibitors) and risk factor modification are ideal agents as they favorably impact the entire coronary tree, not just foci or regions, and as a result, remain necessary and important regardless of the revascularization strategy used. Underlying the results of trials summarized by composite primary endpoints are complex tradeoffs between treatment strategies. How patients and physicians weigh diverse outcomes—early mortality versus late mortality, periprocedural stroke, need for repeat procedures, angina relief, and quality of life—will continue to drive informed patient-decision making aided by all of the members of the clinical team including the internist, general cardiologist, interventional cardiologist, and cardiac surgeon. The ability to select functionally significant lesions may not just reduce the occurrence of adverse cardiac events, but may also improve important patient-related outcomes such as relief of angina, and may avoid unnecessary procedures. Thus, the method of FFR should be considered as a mainstream strategy of treatment among patients evaluated with multivessel disease. By allowing more rational lesion selection based on physiology and not simply angiography, FFR may certainly improve outcomes for diabetic patients.

CONFLICTS OF INTEREST

None declared.

REFERENCES