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EDITORIAL COMMENT

Diabetes in Myocardial Revascularization for Left Main Coronary Artery Disease

Predictor or Decision Maker?*

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In patients with diabetes mellitus (DM), compared with those without DM, the anatomic features of coronary artery disease (CAD) tend to be more diffuse and complex with a rapidly progressive form of atherosclerosis that is associated with increased cardiovascular events and mortality (1). In daily clinical practice, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are the recommended revascularization strategies for diabetic patients with obstructive CAD. In particular, CABG is considered to be the preferred revascularization method for diabetic patients with multivessel or complex CAD (2,3). As such, among several clinical risk factors, DM has been regarded as a major determinant for predicting poor prognosis and has played a pivotal role in the selection of myocardial revascularization methods (4).

Among various forms of obstructive CAD, left main coronary artery (LMCA) disease is associated with high morbidity and mortality owing to the large amount of jeopardized myocardium. Recent evidence indicates that PCI is a safe and effective modality as CABG in patients with LMCA disease with low-to-intermediate anatomic complexity (5-7). However, until recently, there have been limited data regarding the impact of DM on the relative treatment effect of PCI and CABG, and on decision-making of a particular revascularization strategy for LMCA disease. This issue has important implications for the selection of the most effective therapy in this high-risk group of patients.

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This dilemma is addressed in this issue of the *Journal* by Milojevic et al. (8), who performed a major subgroup analysis of the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial to determine the effect of DM in patients with LMCA disease treated with PCI or CABG. Among 1,905 randomized patients, 554 patients (29%) had DM: of these, 27% were receiving insulin therapy, 65% were receiving oral hypoglycemic agents, and 9% were being treated with nonpharmacological measures. Compared with patients without DM, patients with DM were more likely to be obese and have a higher risk of clinical risk-factor profiles and anatomic complexities. As expected, diabetic patients had a significantly higher 3-year rate of the primary composite endpoint of death, myocardial infarction (MI), or stroke than did nondiabetic patients (hazard ratio [HR]: 1.60; 95% confidence interval [CI]: 1.26 to 2.04). DM was an independent predictor for the primary endpoint after both CABG and PCI. The 3-year rate of primary endpoint was similar after PCI and CABG in diabetic patients (HR: 1.03; 95% CI: 0.71 to 1.50) and in nondiabetic patients (HR: 0.98; 95% CI: 0.73 to 1.32). There was no significant interaction between diabetes status and revascularization type for primary endpoint (p for interaction = 0.82) or any secondary endpoints of death (p = 0.22), stroke (p = 0.17), MI (p = 0.99), repeat revascularization (p = 0.68), or the composite of death, MI, stroke, or repeat revascularization (p = 0.65). In addition, there were no significant interactions between insulin use, revascularization modality, and 3-year outcomes among

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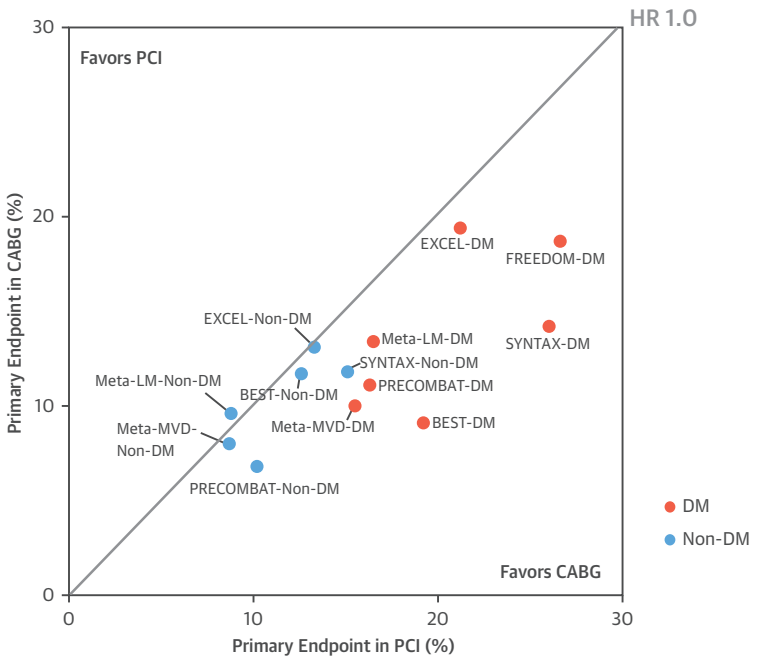
FIGURE 1 Hazard Ratios for the PCI Compared With the CABG Group According to Diabetic Status



Trial	Primary Endpoint	Hazard Ratio		P-Interaction
		DM	Non-DM	
Multivessel CAD				
SYNTAX (N = 1,800)	Composite of death, MI, stroke, or repeat revascularization	1.83 (1.22–2.73)	1.28 (0.97–1.69)	0.12
FREEDOM (N = 1,900)	Composite of death, MI, or stroke	<2 yr: 1.11 (0.85–1.45) >2 yr: 2.06 (1.41–3.02)	NA	NA
BEST (N = 880)	Composite of death, MI, or TVR	2.24 (1.25–4.00)	1.07 (0.65–1.76)	0.06
Left Main CAD				
PRECOMBAT (N = 600)	Composite of death, MI, stroke, or TVR	1.43 (0.65–3.16)	1.51 (0.76–2.99)	0.92
EXCEL (N = 1,905)	Composite of death, MI, or stroke	1.04 (0.70–1.55)	0.97 (0.72–1.30)	0.77
NOBLE (N = 1,184)	Composite of death, MI, stroke or repeat revascularization	15% DM, NA	NA	NA
IPD Meta-Analysis (11 RCT) (N = 11,518)				
Multivessel disease (N = 7,040)	All-cause death	1.48 (1.19–1.84)	1.08 (0.86–1.36)	0.045
Left main disease (N = 4,478)	All-cause death	1.34 (0.93–1.91)	0.94 (0.72–1.23)	0.13

BEST = Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DM = diabetes mellitus; EXCEL = Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM = The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; HR = hazard ratio; IPD = individual patient-level data; LM = left main; MI = myocardial infarction; NA = not available; NOBLE = Nordic-Baltic-British Left Main Revascularization Study; PCI = percutaneous coronary intervention; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RCT = randomized controlled trials; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery; TVR = target-vessel revascularization.

diabetic patients. Despite the inherent limitations of subgroup analyses, this insightful subgroup report provides important context for when revascularization is deemed to be necessary in patients with LMCA disease and DM: the key findings do not support a differential prognostic impact of DM or its current role as the decision-maker for choosing a specific revascularization approach for LMCA disease.

When evaluating the clinical utility of key determinants or risk factors for patients undergoing myocardial revascularization, 2 major aspects should be considered: 1) predicting the risk of future clinical events; and 2) guiding clinical decision-making regarding the optimal revascularization approach. In the EXCEL trial, DM was an independent predictor of adverse events after either CABG or PCI. However, the most important aspect of specific characteristics for clinical decision is the interaction effect, because it drives decision-making between CABG and PCI (9). If a significant interaction is present, the clinical or anatomic factor aids in choosing the intervention, either CABG or PCI, that is most likely to provide the best outcome. However, DM showed no significant interaction effect with CABG and PCI in establishing long-term clinical outcomes in the EXCEL trial. These findings suggest the limited role of DM as a key factor for the optimal decision-making of LMCA revascularization strategies. Even in the SYNTAX trial, DM was shown not to be an independent predictor of mortality in either the CABG or PCI groups and also lacked an interaction effect (9); this is why DM was excluded from SYNTAX score II.

For a long time, >20 years, it has been regarded as conventional wisdom in the cardiovascular community that DM is a critical factor definitely favoring CABG over PCI for complex or multivessel CAD on the basis of a historical and legendary report of the BARI (Bypass Angioplasty Revascularization Investigation) trial (5-year survival in DM: 81% for CABG vs. 66% for PCI; $p = 0.003$) from the balloon angioplasty era (10). Recently, extended follow-up (median 7.5 years) of the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial shows that coronary revascularization with CABG leads to lower all-cause mortality than with PCI in diabetic patients with multivessel CAD (11). However, until recently, the clinical utility of DM as an important decision-maker for a specific revascularization approach was not obvious in recent trials comparing CABG and PCI with drug-eluting stents (**Figure 1**), except for a subgroup with multivessel CAD and DM in a pooled analysis of individual patient data (6). Given that DM has modest discrimination capability for mortality and major cardiovascular events in patients with LMCA disease, the clinical and practical impact of DM as a key factor guiding the revascularization choice should be further debated. Such limited capacity of DM for discriminating comparative outcomes and for decision-making for LMCA revascularization might be explained by a few reasons: First, the revascularization gap in favor of CABG over PCI for diabetic patients has narrowed with incremental improvements in PCI devices (from balloon angioplasty to bare-metal and drug-eluting stents), technology, experience, and adjunctive drug therapies (12). Second, advanced and rapidly evolving optimal medical therapy and diabetes management might also attenuate the treatment gap of the revascularization methods (13).

Decision making between PCI and CABG in patients with LMCA disease should take into consideration several clinical or anatomic aspects and patient preference (14). The selection of PCI or CABG should depend on the risk-benefit ratio of each revascularization strategy, balancing periprocedural major adverse events as well as long-term benefit for mortality or serious clinical outcomes. PCI is a reasonable treatment strategy for diabetic patients with LMCA disease and relatively noncomplex coronary anatomy, whereas CABG is the standard of care for diabetic patients with more complex CAD. Of note, diabetic patients with LMCA disease should be informed about the importance of a heart team approach in determining the optimal treatment and procedural aspects of both PCI and CABG. The take-home message from this major substudy of the EXCEL trial is that DM is an important determinant of long-term outcomes after coronary revascularization; however, DM is not a strong discriminator for guiding the optimal revascularization approach. In a contemporary clinical setting, DM is a good predictor of outcomes, but not a clear decision-maker for the best revascularization method for significant LMCA disease.

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