

## EDITORIAL COMMENT

# Diabetes Mellitus Does Not Unsweeten Left Main Intervention\*

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Andreas Gruentzig frowned on balloon angioplasty for unprotected left main coronary artery (LMCA) disease. One of his earliest cases was such a patient. And why not? During the early years, the paramount challenge for balloon angioplasty was achieving acute success—namely, dilating the lesion. Reaching and crossing a lesion were the most demanding parts of the procedure. Given this, the left main with its proximity and short, straight course was a natural target. His first left main attempt was successful, for the short term. Despite relief of angina and normalization of his stress test, the patient died suddenly early in follow-up. Lesion recurrence was the putative culprit, and subsequently LMCA angioplasty was contraindicated, because restenosis might express itself as sudden death.

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Over the last several years, our view of unprotected LMCA percutaneous coronary intervention (PCI) has changed. There have been several large observational reports of consecutive patients, carefully selected and treated with refined stenting technique, that demonstrate 1-year mortality rates as low as 4.8%. Importantly, in-hospital mortality rates are 0% in many series, indicating that the real concern for untoward events related to LMCA PCI resides in the period of follow-up (1,2).

More recently, the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) randomized study confirmed these favorable outcomes in patients with LMCA disease (3). In patients randomized to PCI the peri-procedural death rate was 0.1%, and 1-year mortality was 4.4%. The SYNTAX investigators made several significant observations about

unprotected LMCA disease. First, in the subset of patients that had LMCA disease, there was no significant difference in composite rate of major adverse cardiac or cerebrovascular events at 1 year between the PCI and coronary artery bypass grafting (CABG) groups (15.8% vs. 13.7%,  $p = 0.44$ , respectively). Rates of repeat revascularization, however, were significantly higher among PCI patients (11.8% vs. 6.5%,  $p = 0.02$ ), whereas stroke was more common among CABG patients. These data support the use of PCI with drug-eluting stents (DES) as a reasonable alternative to CABG for patients with LMCA disease. A second observation, however, qualifies this conclusion. When SYNTAX investigators analyzed outcomes according to LMCA disease involvement and the extent of associated coronary disease, they identified a relationship between disease distribution and PCI outcome. For unprotected LMCA patients with limited disease (i.e., 0- or 1-vessel disease), the observed rates of adverse events at 12 months trended lower in the PCI group than in the CABG group. For patients with unprotected LMCA and 2- or 3-vessel disease, the opposite was true, with rates of adverse events higher in PCI patients. In summary, the SYNTAX study did not identify a safety concern of PCI for unprotected LMCA for up to 12 months of follow-up. The primary shortcoming of PCI during this period was the excessive need for a repeat revascularization procedure. Of note, 25% of patients in the SYNTAX trial had diabetes mellitus.

The presence of diabetes mellitus has influenced the comparative effectiveness of PCI and CABG. In the BARI (Bypass Angioplasty Revascularization Investigation), multivessel coronary artery disease patients with diabetes who were randomly assigned to PCI had a higher 5-year mortality rate than similar patients assigned to CABG. Furthermore, in the absence of diabetes, rates of death and myocardial infarction (MI) were independent of revascularization strategy (4). On the contrary, patients in the BARI registry did not demonstrate this influence of diabetes on outcome (5). These findings might be explained by the relative contribution of patient factors, anatomic disease severity, and physician judgment in recommending an appropriate revascularization strategy.

In this issue of *JACC: Cardiovascular Interventions*, Kim et al. (6) report on the influence of diabetes on the outcomes of unprotected LMCA patients treated with either DES or CABG within the MAIN-COMPARE (Revitalization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry (2). This is a particularly relevant topic. First, patients with diabetes are more likely to experience restenosis, a potentially fatal event for those with unprotected LMCA disease treated by PCI. Second, diabetes is associated with more advanced and complex coronary artery disease, a setting wherein PCI is less effective.

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In their registry of 1,474 patients, 507 had diabetes. Kim et al. (6) found meaningful differences in the distribution of baseline features between the PCI and CABG groups, for the most part indicating CABG patients had more severe disease. Such an imbalance and the nonrandomized study design substantially limit our ability to directly compare the effectiveness and safety of the 2 revascularization options. As expected, unadjusted rates of death, MI, stroke, and target vessel revascularization (TVR) were higher at 3 years in patients with diabetes compared with those without. Among patients with diabetes, there were no differences in estimated, unadjusted rates of death, Q-wave MI, or stroke according to revascularization treatment. As usual, there was a substantial difference in TVR favoring CABG (2.0% vs. 11.2%,  $p < 0.001$ ). Importantly, however, the significantly higher rate of TVR with PCI was also observed in patients without diabetes mellitus, suggesting that additional factors are responsible for the increased rate of TVR in PCI patients. This is supported by the finding that treatment effects for PCI and CABG did not vary according to diabetes status. After statistical adjustment, differences in outcomes were similar. Thus, with repeat revascularization aside, PCI can provide a safe alternative to CABG for a substantial proportion of patients with unprotected LMCA disease and diabetes.

It is important to consider case selection, when putting the study results in perspective. An interesting observation is that diabetes status seemed to play only a minor role in determining whether PCI or CABG was selected as the initial revascularization strategy in this group of registry patients. Of the 507 patients with diabetes, 50% of patients received DES, and 50% underwent CABG. In nondiabetic patients, DES was chosen only slightly more frequently at 55%, with 45% undergoing CABG. This observation is not entirely new. A prior study in stable angina patients found that treatment decisions regarding the choice for CABG or PCI were not influenced by the presence of diabetes (7). In the BARI type-2 diabetes trial (8), selection of CABG over PCI was declared in 44% of patients and was driven primarily by characteristics determined by the coronary angiogram.

Both anatomic and patient-related factors have been shown to influence the outcome of unprotected LMCA disease PCI, and although we are not provided the details regarding treatment decisions in this study, the data speak to these issues. Prior unprotected LMCA PCI studies observed a high mortality rate in high-risk patients as determined by the European system for cardiac operative risk evaluation (Euroscore) (9,10). In this study, the Euroscore was higher in patients chosen for CABG compared with PCI. With respect to anatomic factors, PCI patients with isolated unprotected LMCA disease and those with-

ostial or proximal LMCA disease have much better outcomes than those with complex distal LMCA bifurcation or associated multivessel disease, where a disproportionately high incidence of restenosis has been observed (1,3,11,12). In the current study, PCI patients were more likely to have isolated LMCA disease. Although ostial and mid shaft disease was less common in the PCI patients, those with distal bifurcation disease involvement less often had involvement of both the ostial left anterior descending and left circumflex coronary arteries. In other words, among the PCI patients, the distal LMCA disease was less complex. This is confirmed by the low number of stents used ( $1.3 \pm 0.6$ ) in those with diabetes.

A final comment is that the influence of post-PCI surveillance cannot be overlooked and that outcomes must always be interpreted within the context that they are gathered and reported. For a registry study where individual physicians are responsible for clinical follow-up, there might be tremendous variation in the frequency and modalities of post-PCI evaluation. A shortcoming is that we are not provided with information on the number of patients that underwent routine surveillance angiography or the indication for repeat revascularization. The majority of TVR events in the PCI patients seem to occur between 6 and 12 months. There are many physicians that believe that unprotected LMCA PCI patients should be followed with routine angiography during the first year, and this has been considered acceptable in the PCI guidelines (13). Surveillance angiography in unprotected LMCA PCI increases TVR (12), as is the case in other PCI scenarios. Nevertheless, the 1-year rates of PCI reported by Kim et al. (6) are more than acceptable and in line with the SYNTAX trial.

How does this report affect our current indications for selecting PCI or CABG for an individual patient with unprotected LMCA disease? The current American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines state that CABG is the preferred revascularization approach for such patients and that PCI should only be offered when surgery is not feasible or excessively hazardous (13). It is likely that enough evidence exists to warrant a change in this recommendation, on the basis of multiple observational studies, the SYNTAX study, and personal experiences. It seems reasonable to offer PCI to selected unprotected LMCA disease patients with minimal associated vessel disease and simple lesions. Presence of diabetes should not affect this decision. This recommendation is tempered, however, in that legitimate comparative long-term data are not available. Moreover, we should not hastily abandon this established method of revascularization, given the recognized survival benefit of CABG for patients with unprotected LMCA disease.

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**Key Words:** diabetes mellitus ■ left main coronary artery disease ■ stents ■ coronary artery bypass surgery.