EDITORIAL COMMENT

Silent Ischemia: Unsafe at Any Time*

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Percutaneous coronary intervention (PCI) using balloon angioplasty with stenting has become a mainstay in the treatment of patients with coronary artery disease (CAD). Over one million PCI procedures were performed in the U.S. alone in 2000, nearly one-half of which involved placement of a coronary stent (1). This number is expected to increase as more revascularization procedures that were previously thought to be surgical are now approached with angioplasty and stents.

Although many of the initial limitations of PCI have been overcome by improvements in equipment and antiplatelet therapies, restenosis continues to be a major problem. Although restenosis rates have been significantly reduced with the use of stents (2,3), even when stents are used, restenosis rates in excess of 50% can be observed (4). In addition, progression of disease in untreated vessel segments remains an important problem for patients with CAD following any type of revascularization, occurring at rates approaching 7% per year (5).

In the Lescol Intervention Prevention Study (LIPS), the overall rate of major adverse cardiac events (MACE), defined as death, nonfatal myocardial infarction (MI), or re-intervention, was >6% per year over 3.9 years of follow-up in patients undergoing a first PCI (6). Although treatment with aggressive cholesterol-lowering therapy significantly reduced the MACE rate, the combined incidence of cardiac death and nonfatal MI in the treated cohort was still 1.3% per year in this population with a relatively early stage of CAD. A comparison of the 1997 to 1998 Dynamic Registry and the 1985 to 1986 National Heart, Lung, and Blood Institute Registry of patients undergoing an initial PCI procedure revealed that one-year crude mortality was actually higher among patients in the more recent study (5.4%) than in the earlier registry (3.6%), particularly among women (8%), despite higher procedural success rates and lower rates of coronary artery bypass grafting (CABG) (7). Only after adjusting for baseline differences (i.e., age >65 years, history of diabetes or congestive heart failure [CHF], circumstances of the procedure, and more revascularization procedures involving totally occluded vessels and vein grafts) were mortality rates for the two registry cohorts comparable and the risk for the combined end point of death or MI less for the Dynamic Registry cohort. However, the reality of contemporary interventional practice is that patients having the very characteristics necessitating this adjustment comprise an increasing percentage of the population undergoing PCI. The average patient now undergoing PCI is at a higher risk for cardiovascular events following the intervention than were patients treated with PCI in the past (7).

Although the presence or absence of chest pain can serve as a basic form of risk stratification among patients who have undergone revascularization, chest pain has repeatedly been found to have low sensitivity for the detection of restenosis and myocardial ischemia following PCI (3,8–13). Indeed, silent ischemia has been found to occur in nearly 60% of patients following percutaneous transluminal coronary angioplasty (PTCA) (9) and in a similar number of patients (58%) after stenting (3). Importantly, the presence of chest pain prior to PCI does not correlate with the recurrence of symptoms due to restenosis (3,10,13), nor does the presence of chest pain after PCI correlate with the presence of restenosis (8,14).

It has been well established that silent myocardial ischemia is associated with poorer outcomes in patients who have not undergone PCI. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, both mortality (4%) and the combination of death or MI (9%) at one year were significantly greater among patients assigned to angina-guided medical therapy than among patients assigned to a revascularization strategy (0% and 3%, respectively), despite the fact that 23% of patients in the medically treated arm underwent nonprotocol revascularization (15). There is no "a priori" reason to believe that silent ischemia is less ominous in patients who have undergone PCI. However, the use of noninvasive testing and directed re-intervention following PCI have never been systematically investigated.

Pfisterer et al. (12) followed 109 patients with angiographically documented restenosis who had evidence of ischemia on planar thallium-201 imaging performed six months following PTCA; ischemia was silent in 61%. After two years, the event rate was significantly greater in patients with silent ischemia who did not undergo re-intervention (17%) than in patients without ischemia (8%). Cottin et al. (14) prospectively studied 152 patients who underwent coronary stent placement and myocardial perfusion single-photon emission computed tomography (SPECT) five months later. After 40 months of follow-up, the rates of cardiovascular death and MI were significantly lower among patients without (1% and 2%, respectively) versus with (15% for both) ischemia, based on stress myocardial perfusion imaging (MPI). Importantly, 60% of patients with ischemia...
were asymptomatic. Angina was not an independent predictor of cardiovascular death or MI.

The study reported by Zellweger et al. (16) in this issue of the Journal is an important one which further extends the earlier observations from this group and helps define the true incidence of silent ischemia in patients undergoing PCI, as well as the role of silent MPI in defining ischemia. This study summarizes the follow-up of 307 patients who underwent stress MPI six months after stenting for a minimum of 3.2 years to ascertain the incidence of silent versus symptomatic ischemia after stenting, predictors of silent versus symptomatic ischemia, predictors of long-term outcome vis a vis symptomatic status, and the incremental value of stress MPI over clinical and stress testing variables. They also present follow-up data for an additional 17 patients who underwent re-intervention as a result of the six-month stress MPI study, as well as for 32 patients with evidence of ischemia in untreated territories on the six-month MPI study.

Six months after PCI, 32% of patients had evidence of myocardial ischemia by stress MPI. Ischemia was located in the target vessel territory in 72% of these patients and in a remote territory in 28%. Of 68 patients with chest pain six months after stenting, 37% had no evidence of ischemia by stress MPI. Conversely, 81 patients with target vessel ischemia documented by MPI, only 38% had angina. Thus, ischemia was silent in 62% of patients with target vessel ischemia six months after PCI, 66% of these patients had angina before stenting. Of the 32 patients with ischemia in an untreated territory, 59% had silent ischemia. Patients with silent target vessel ischemia had fewer CAD risk factors, were less likely to have hypertension or previous CABG, had less severely stenotic lesions treated, less often had ischemic stress electrocardiographic (ECG) changes, more often had peri-infarct ischemia, and had less severe and less extensive ischemia on their stress MPI. Thus, their summed stress scores (SSS) and summed difference scores (SDS) were lower.

After a mean follow-up of 4.1 years, the overall rate of the composite end point (all-cause mortality, nonfatal MI, and “late” revascularization) was 22%, whereas the rate of death and nonfatal MI was 8%, or 2% per year. The composite event rate was significantly greater for the 65 patients with target vessel ischemia who did not undergo re-intervention (38%) than for the 242 patients without ischemia (17%), although this difference was primarily driven by repeat revascularization. Event rates for both patients with silent ischemia and for those with symptomatic ischemia were significantly greater than for patients with no ischemia. The best predictors of an adverse outcome were diabetes and extent of ischemia. Although patients with silent target vessel ischemia had less severe and less extensive ischemia, there was no significant difference in outcome between patients with silent and symptomatic ischemia, although there was a trend toward a better outcome for patients in whom ischemia was silent.

The authors also demonstrate the incremental prognostic value of stress ECG over clinical information and of stress MPI over clinical plus stress ECG data. Of the 356 patients in the initial “diagnostic group,” only 19% had angina six months after stent implantation, 13% had nondiagnostic ECG changes during stress, 13% had ischemic ECG changes, and 32% had scan evidence of ischemia. This reaffirms the findings of previous investigations that showed poor accuracy of chest pain and stress ECG changes for the detection of restenosis and ischemia or for the prediction of the occurrence of adverse cardiac events (8,10,12–14,17).

The accuracy of stress MPI for the detection of restenosis has been found to range from 79% to 89% when performed six or more months after PCI with or without stenting (10,17,18). The incidence of asymptomatic restenosis following coronary stenting has been found to range from 30% to 58% in studies using angiography (2,3). Thus, the percentages of patients with silent ischemia reported in the study by Zellweger et al. (16)—62% for those with target vessel ischemia and 59% for those with ischemia in an untreated territory—are slightly above the rates found using invasive methods. This would suggest that the definition used by Zellweger et al. (16) to define ischemia (i.e., SDS ≥1) is perhaps overly sensitive. Although it may not seem surprising that, in the present study, patients with silent ischemia had less severe and extensive perfusion defects, and that SDS ≥4 best separated patients with silent from those with symptomatic ischemia, others have shown that the extent and severity of ischemia are similar in patients with silent and symptomatic ischemia (10,13). Although a low SDS was the most powerful predictor of silent ischemia, the absence of hypertension and greater lesion severity at the time of PCI were also associated with silent ischemia, in agreement with earlier studies (11,19). Importantly, the current investigation also demonstrates that the incidence of silent ischemia is the same in patients with and those without diabetes, in agreement with previous studies (3,11,13).

Zellweger et al. (16) show that defect severity on MPI, not symptomatic status, is the most powerful predictor of adverse events, and that differences in event rates are seen among patients with no ischemia, those with mild ischemia, and those with moderate to severe ischemia. Cottin et al. (14) similarly demonstrated that stress MPI, and not symptom status, best predicted outcome following coronary stenting. The important point made by this study is that, although there was a trend toward better outcomes for patients with silent ischemia, who tended to have less extensive and severe ischemia compared with patients with symptoms, there was no significant difference in outcomes between the two groups, both of which fared worse than patients with no ischemia. Thus, although asymptomatic patients as a group may be less likely to have an adverse event following PCI, the only way to ascertain any particular patient’s risk with certainty is to perform stress MPI. On the other hand, because a significant number of patients with
symptoms had no evidence of ischemia on stress MPI, it could be argued that the only way to accurately ascertain the risk for any particular patient with chest pain following PCI is to perform perfusion imaging. However, an important point to learn from this study is that the event rate for the group of patients with chest pain who did not have ischemia on stress MPI was similar to that of patients with silent ischemia. As no details regarding the former group are provided, it is unclear whether stress MPI in these patients was false negative, what types of events befell them, or whether re-interventions performed were largely symptom-driven.

Important information can also be derived by assessing the outcome of the 49 patients who were excluded from the “prognostic patient” group. Seventeen patients underwent re-intervention at the time of six-month stress MPI; 16 patients had target vessel ischemia and 35% were asymptomatic. The overall event rate in this cohort was 18%, less than that of the cohort with target vessel ischemia who did not undergo stress MPI-driven re-intervention, but similar to that of the nonischemic cohort. Thirty-two patients had ischemia in a nonrevascularized territory at the time of the six-month stress MPI. The MACE rate in this cohort, driven primarily by revascularization procedures, was 25%, or 7% per year, whereas the death rate was 3%.

The major finding of the present study is that silent ischemia occurs frequently after coronary stenting, both as a result of restenosis and disease progression in untreated vascular territories. Patients with ischemia have a worse prognosis than those with normal perfusion, whether ischemia is silent or symptomatic. The long-term outcome is most closely associated with the extent and severity of myocardial ischemia, which can be accurately assessed by stress MPI. Stress MPI adds incremental prognostic information to clinical and stress ECG data in post-PCI patients. There is also suggestive evidence that directed re-intervention, based on stress MPI, can further improve the outcome of patients.

One obvious limitation of this study is the absence of angiographic follow-up. Although highly accurate, stress MPI is neither 100% sensitive nor 100% specific. Given the higher incidence of silent ischemia reported in the current study compared with angiographic studies, it is possible that some patients purported to have silent ischemia actually had a false-positive stress MPI. This would lead to an overestimation of the rate of silent ischemia and an underestimation of the adverse event rate among patients who truly have silent ischemia, by including patients without restenosis. A further limitation of the study is the small number of adverse events in the study cohort, other than re-interventions. Although this is one of the larger studies to examine the outcome of patients with silent ischemia following PCI, because of the low incidence of cardiovascular death and MI in the “prognostic group” (2% per year), the study lacks sufficient power to detect a difference in the occurrence of these important end points. A final limitation of the present study is that patients who underwent re-intervention as a result of the six-month stress MPI were excluded from subsequent analyses. Important information on the impact of stress MPI-driven re-intervention on patient outcome might arise from such an analysis.

This study reconfirms the importance of silent ischemia in post-PCI patients, as well as the likely benefits of directed re-intervention in improving the long-term outcome of this growing patient population. It seems reasonable to suggest that stress MPI, performed six months after PCI, can identify a significant number of patients who are at risk of future cardiac events and who warrant further invasive evaluation and therapy.

References


