Does Preventive PCI Work?

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Treatments are designed to make people feel better or live longer. Percutaneous coronary intervention (PCI) is effective at reducing angina in patients with symptomatic coronary artery disease and at reducing mortality in patients who have acute myocardial infarction with ST-segment elevation and in those who have high-risk acute coronary syndromes without ST-segment elevation. Such successes have often been extrapolated in support of more widespread use of PCI in patients with stable coronary artery disease in hopes of reducing subsequent cardiac events.

With the increasing availability of noninvasive imaging of coronary artery disease, asymptomatic patients are often referred for PCI. But preventive intervention presupposes a threat that can be averted at an acceptable cost. In the case of stable coronary artery disease, the threat is subsequent myocardial infarction and death. The questions are How likely is this threat? And does PCI provide an appropriate answer to it? In this issue of the Journal, in a report on the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE, NCT00007657) trial, Boden et al. provide some answers to these questions. They report that for a large population with stable coronary artery disease, the 4.6-year cumulative rates of myocardial infarction and death were 19.0% in patients who underwent PCI in addition to receiving optimal medical therapy (PCI group) and 18.5% in those who received medical therapy alone (medical-therapy group); the rates of death were approximately 8% in both study groups.

Can these findings be generalized? The large number of patients who were screened for eligibility, as compared with those who were enrolled, raises concern, but the population seems to be representative of patients with stable coronary artery disease who undergo PCI. Most of the patients had preserved ventricular function, and a large majority had angina and multivessel coronary artery disease. Patients whose condition was stable after myocardial infarction were enrolled (38%), and spontaneous or inducible ischemia was required, but patients with severe ventricular dysfunction, clinical instability, or very early ST-segment depression or hypotension on stress testing were excluded. Although the trial had slightly less power than anticipated, the 95% confidence intervals indicate that the chance that PCI yielded a reduction of more than 13% or an increase of more than 27% in myocardial infarction and death is small.

Patients who were enrolled in the COURAGE trial were quite successful at achieving goals for both lipid levels and blood pressure; they had less success in meeting the more difficult objectives of weight loss, smoking cessation, and increased exercise. The use of antiplatelet agents, statins, angiotensin-converting–enzyme (ACE) inhibitors, and beta-blockers was appropriately high in both groups. The nearly 33% of patients who crossed over from medical therapy to revascularization during the 4.6-year period was higher than anticipated, but this does not detract from the finding that initial PCI failed to prevent myocardial infarction and death in this population. Against a backdrop of optimal medical therapy, the trial tested selective PCI for patients with angina that had failed medical management, as compared with preventive PCI for all. The proportion of angina-free patients was modestly but significantly higher at 1 and 3 years in the PCI group (with...
lower use of antianginal medications), but not at 5 years. The substantial increase in the proportion of angina-free patients in the medical-therapy group cannot be ascribed solely to the performance of revascularization during follow-up but appears to derive mostly from intensive control of risk factors (leading to better endothelial function) and antianginal medication. Although quality-of-life data are not yet available, this study confirms previous observations that PCI is effective at relieving symptoms.

Why did PCI fail to reduce events beyond intensive medical therapy? This result was not due to the fact that the COURAGE trial enrolled a low-risk population (the annualized rate of myocardial infarction and death was >4%). In this stable population, the proportion of deaths from cardiac causes was relatively low, but there are pitfalls in the classification of death. The 2.8% of patients who had periprocedural myocardial infarction (clinical events with an increase in levels of biochemical markers by a factor of more than 3 for the creatine kinase MB fraction and more than 5 for troponin) is within the reported range, but some observers may consider the rate high for a population with stable angina. However, this category includes patients with repeat PCI events, and often multiple lesions were dilated. Also, 38% of patients had had a previous myocardial infarction (in an unknown percentage, the myocardial infarction was recent) and therefore were at higher risk for early events. During the study period, there was a change in clinical practice to more aggressive clopidogrel regimens before and after PCI procedures, and the effect of this change on the frequency of myocardial infarction is unknown. There was an excess of only 26 periprocedural myocardial infarctions in the PCI group, and exclusion of all periprocedural myocardial infarctions (an unrealistic clinical scenario) still reveals no significant benefit for PCI.

Despite the widespread belief that PCI may reduce the incidence of cardiac events, the findings of this study are understandable. Tight stenoses, responsible for stable angina, are a marker for many more nonobstructive, lipid-laden lesions, which are also at risk for inflammation and rupture and therefore have a cumulatively higher likelihood of triggering an acute coronary syndrome and sudden death. Since the risk of coronary occlusion is not proportional to the previous severity of stenosis, it is not surprising that treating one or more stable, tight lesions did not reduce rates of subsequent myocardial infarction and death. The effectiveness of intensive modification of risk factors that was observed in the COURAGE trial is consistent with the secondary prevention observed with aggressive lipid-lowering therapy in coronary artery disease. Lipid-lowering therapy has been shown to be more successful at reducing cardiac events than at reducing the severity of stenosis, presumably through improved endothelial function and plaque stabilization.

The findings of the COURAGE trial are consistent with those of previous smaller studies involving patients with stable coronary artery disease, which reported no reduction in myocardial infarction and death with PCI but a reduction in angina. The COURAGE trial was the first to use stents routinely along with what has now become optimal medical therapy. Although drug-eluting stents reduce the need for repeat revascularization, they have not been shown to reduce myocardial infarction and death, as compared with bare-metal stents, and there is concern about late stent thrombosis. However, the rate of repeat revascularization is consistently lower with drug-eluting stents. Hence, their use in the COURAGE trial would probably have translated into a rate of repeat revascularization that was lower than the reported 21%, and possibly less angina.

Despite the lack of significant interaction between subgroups of patients and the effect of PCI on myocardial infarction and death, there will be a temptation to overinterpret data from subgroups in search of one in which benefit from PCI is suggested (on the basis of sex, type of hospital, or a combination of high-risk variables). Unfortunately, the proportion of women and nonwhite patients was small in this study. But the pitfalls of subgroup analyses (multiplicity, smaller size, and confounding) are well known. Although there were only 406 patients with an ejection fraction between 30 and 50%, there was no suggestion of treatment interaction. Additional data are needed in patients with depressed ventricular function and in women.

Would surgical revascularization have fared better than PCI? The trials comparing medical therapy with surgery are old and relatively small. As for PCI versus surgery, guidelines...
rize the trial evidence as suggesting that for most patients either procedure is an effective option for the treatment of symptoms, and both are associated with similar long-term outcomes. Some high-risk patients, however, may do better with surgery.

The COURAGE trial adds to the still limited body of evidence for strategy selection in coronary artery disease. Trials involving patients with diabetes and those with heart failure and severe ventricular dysfunction are ongoing. The recent Occluded Artery Trial (OAT, NCT00004562), which showed no benefit for PCI, provided information on patients whose condition is stable after myocardial infarction with persistent occlusion of the infarct artery.15

The COURAGE trial should lead to changes in the treatment of patients with stable coronary artery disease, with expected substantial health care savings. PCI has an established place in treating angina but is not superior to intensive medical therapy to prevent myocardial infarction and death in symptomatic or asymptomatic patients such as those in this study. Secondary prevention has proved its worth, with lipid-modulating therapy, lifestyle modification, and the use of aspirin, beta-blockers, and ACE inhibitors. Patients whose condition is clinically unstable, who have left main coronary artery disease, or in whom medical therapy has failed to control symptoms remain candidates for revascularization, but PCI should not play a major role as part of a secondary prevention strategy.

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