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EDITORIAL COMMENT

The Challenge of Left Main Stenosis*

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The purposes of invasive, anatomic treatments for patients with coronary atherosclerosis are to relieve symptoms and to prolong life expectancy. When the patient's issues revolve around symptom status, that patient advises the physician of their symptomatic level, the extent to which these symptoms limit their life, and the physician then advises the patient about treatment options. If one treatment does not work, another is usually available. When the issue is life expectancy, the situation is different. Physicians bear the responsibility for advising the patient about the future likelihood of death, an irrevocable event, associated with various treatment strategies. The higher the risk of death associated with the condition, the greater the responsibility for accurate recommendations about the future and the greater the importance of the data physicians base those recommendations on.

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Randomized and nonrandomized trials have shown that bypass surgery prolongs the life expectancy of patients with severe coronary artery disease when compared with medical therapy (1,2). The clear demonstration of the survival benefit of surgery does not apply to all patients even with multivessel disease but specifically to high-risk subsets including patients with a positive stress test, abnormal left ventricular systolic function, a proximal left anterior descending coronary artery stenosis, and left main coronary artery disease. Left main coronary artery stenosis, in particular, has been repeatedly documented to have a high association with death in the absence of anatomic treatment (1).

Percutaneous coronary intervention (PCI) has been shown to improve the life expectancy of some subsets of patients with acute coronary syndromes when compared with medical therapy. The impact of PCI on the life expectancy of patients with chronic coronary artery disease is less assured, and multiple trials and analyses have been conducted with the goal of establishing the principle that the use of PCI as an initial invasive therapy does not compromise long-term survival. Randomized trials comparing PCI and surgery in the treatment of low-risk patients with chronic coronary artery disease have shown either no difference in survival or a small advantage for surgery. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, a trial randomizing relatively low-risk patients (with, however, a high incidence of proven ischemia) to PCI versus optimal medical therapy has shown no survival advantage for PCI to date. Retrospective observational risk-adjusted studies comparing PCI and surgery, and inclusive of heterogeneous patient samples spanning multiple risk categories such as the reports from the New York State database, do appear to show survival differences in favor of surgery (3). These differences increase with time, increase with increasing extent of coronary artery disease, and have been persistent into the era of drug-eluting stents (4). The New York State registries have excluded patients with significant left main coronary artery stenosis.

The study reported by White et al. (5), in this issue of *JACC: Cardiovascular Interventions*, is a single-center retrospective observational risk-adjusted study comparing PCI and surgery for the treatment of chronic coronary atherosclerosis in patients with left main stenosis. The authors, and others, have demonstrated that the procedural safety of stenting for left main stenosis is consistently achievable. However, the demonstration of the long-term safety of stenting as an anatomic treatment for left main stenosis has not been achieved by these data. The current study does not contain enough patients followed for long enough to establish the principle that left main stenting is protective against the end point of death. The mean follow-up of patients after PCI in this study was <1 year and that of surgically treated patients <2 years. The report does not list the number of death and events that occurred, but it appears that the total number of deaths that occurred in the surgical group was about 11 and those after PCI was about 28. The number of events determines the effective sample size, and the number of events in this sample size is effectively very small.

These are not just technical details, as the sample size impacts strongly on conclusions about statistical significance and appears to account for some apparent dilemmas concerning the data. A cursory glance at the report survival curves detects trends toward advantage for the surgical groups that are not statistically significant. The risk-adjusted relative risk of mortality of PCI over that of surgery was nearly 2-fold (1.93) but was not statistically significant ($p = 0.10$), whereas a lesser relative risk (1.83) of major adverse cardiovascular and cerebrovascular events was significant ($p = 0.05$). This difference is entirely based on an increased number of events.

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These types of considerations may also explain the apparent discrepancy between the "high-risk" group who experienced improved survival with surgery and the "lower-risk" group whose survival was equivalent. The lower-risk patients overall have fewer events out to 30 months after operation, and even if mortality is doubled in the PCI group, differences are not apparent at that time interval. "High-risk" patients experience more events overall, and with a similar increase in risk after PCI, the differences in outcomes become more apparent. In studies of mortality comparing varying surgical strategies, such as vein grafting versus internal mammary artery grafting, it has often been noted that "lower-risk" patients just take a longer time for risk differences to become apparent.

The identification of risk categories is itself a complex undertaking and will be important in the construction and analyses of randomized trials studying the impact of treatment on patients with left main stenosis. In this study, risk stratification groups were developed with data pertaining to surgically treated patients. Certainly, this is a reasonable place to start since comparable data do not exist regarding the treatment of patients with left main stenosis with PCI, but variables impacting on risk with surgical treatment may be different than those impacting on risk after PCI. Indeed, the authors believe this to be true since the patients selected for surgery and selected for PCI were different in many ways. It is notable concerning this study, however, that the anatomic extent of coronary disease did not appear to be included in the propensity score or other risk factor analyses. This is surprising since we have identified the anatomic extent of coronary disease as a factor impacting on the surgical risk of the treatment of patients with left main stenosis, and it would seem intuitively that the extent of disease might affect long-term PCI outcomes even more than surgical outcomes (6). Late clinical events after PCI have been shown to often be related to anatomic events in nonstented but atherosclerotic coronary segments. It is not impossible to imagine that left main stenting might be an effective treatment for isolated left main stenosis considering the decreased risk of restenosis associated with the drug-eluting stent-clopidogrel strategy. Most patients, however, do not have isolated left main stenosis, and the impact of more extensive disease on long-term outcome will be important to assess.

Tremendous strides have been made in the safety of all types of coronary interventions including those for left main stenosis, and the decrease in stent-related restenosis associated with drug-eluting stents is well documented and important, even though the impact of the use of drug-coated stents on survival is still uncertain (7). The advances offer opportunities. One opportunity may be left main stenting for patients also undergoing bypass grafting in an attempt to ameliorate the long-term incremental risk for left main stenosis. Another may be the total interventional treatment for subsets of patients with left main stenosis as described in this study. Further follow-up of the patient subsets studied in this report by the authors will produce a valuable resource. In the foreseeable future, it is likely that the interventional and surgical treatment of left main stenosis will be complementary. The challenge will be to dissect out those subsets of patients who fare particularly well with interventional treatment or particularly well with surgery. This task will require large patient subsets, long follow-up, and careful analyses. The procedure-related morbidity of bypass surgery is an important disadvantage for many elderly patients, as pointed out by the authors. The disadvantage of stenting relates to the life-threatening character of left main stenosis and the uncertainty concerning the positive impact of stenting for these patients. It is logical to believe that left main stenting will help to prolong life expectancy in some patient subsets. Our challenge is to identify who those patients are.

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