EDITORIAL COMMENT
Surgery, Angioplasty, or Medical Therapy for Symptomatic Multivessel Coronary Artery Disease

Is There an Indisputable “Winning Strategy” From Evidence-Based Clinical Trials?*
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We all like to embrace winning strategies for patient management in cardiovascular therapeutics. These strategies are important because we are so often besieged with a spectrum of treatment options, and both patients and their families, as well as referring physicians, implicitly put their trust in our specialized knowledge to make well-informed decisions that impact favorably both symptomatic improvement (quality of life) and event-free survival (quantity of life). The optimal management of stable angina patients with symptomatic multivessel coronary artery disease (CAD) remains multi-dimensional, but therapeutic options include aggressive medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery.

What can we learn from the wealth of randomized clinical trials over the past 30 years that have rigorously evaluated myocardial revascularization (CABG or PCI) as an initial treatment strategy compared with medical therapy in stable CAD patients and, can we identify treatment strategies that are clear winners—or losers?

In the 1970s, the role of CABG surgery versus medical therapy (largely nitrates and/or beta-blockers) was assessed prospectively in three separate multicenter, randomized clinical trials (RCTs): the Veterans Administration Cooperative Study of patients with chronic stable angina (1), the European Coronary Surgery Study (2), and the Coronary Artery Surgery Study (3). On the basis of these pivotal trials, we can conclude convincingly that CABG surgery is the treatment of choice for patients with significant obstruction of the left main coronary artery, triple-vessel CAD and left ventricular (LV) systolic dysfunction, and two-vessel CAD plus proximal left anterior descending coronary artery (LAD) stenosis (1–3); not only was CABG surgery superior to conventional (1970s) medical therapy for angina relief, it also conferred a significant survival advantage. Moreover, a meta-analysis of the three major trials and some smaller ones showed a significant survival benefit for patients with triple-, double-, or even single-vessel CAD patients that included a proximal LAD stenosis, with or without abnormal LV function (4). Thus, we can say that, for many CAD patients with stable angina, CABG surgery compared with medical therapy improves both the quality and quantity of life. Coronary artery bypass graft surgery is a clear winner...

Percutaneous coronary intervention has become almost universally embraced as the preferred revascularization strategy for CAD patients in the U.S., where now more than 1 million such procedures are performed annually. No less than 10 RCTs have evaluated PCI versus CABG surgery as an initial strategy of managing stable angina patients and some have reported long-term results (5–7). Overall, these trials suggest that PCI is slightly less effective at relieving angina than is CABG surgery, but there is no compelling evidence that either revascularization strategy provides a prognostic advantage (i.e., reduces significantly the incidence of myocardial infarction [MI] or death) in the majority of CAD patients. More recently, several trials of multivessel stenting versus CABG surgery have shown comparable results to earlier studies of balloon angioplasty versus surgery and suggest that certain subsets of patients, notably diabetics, may benefit from stenting, but their follow-up periods are still relatively short. And even with the recent introduction of drug-eluting stents, there is a paucity of data in many subsets of CAD patients (i.e., diabetics, those with small coronary vessel diameter, complex anatomy, and so on) and virtually no long-term data to assess the efficacy and durability of these newer technologic advances on reducing “hard” clinical end points. Thus, at present, PCI for patients with multivessel CAD cannot be considered a clear “winner” compared with CABG surgery. But, what about PCI or CABG surgery compared with medical therapy in such patients?

In this issue of the Journal, Hueb et al. (8) report the one-year follow-up results of the second Medicine, Angioplasty, or Surgery Study (MASS-II), which randomized 611 stable angina patients with multivessel CAD to CABG surgery, PCI, or medical therapy. In this relatively small, single-site study, the authors demonstrated a statistically significant lower rate of one-year mortality in the medical therapy group (1.5%), whereas the death rates for the PCI (4.5%) and CABG surgery (4.0%) groups were comparable. The rate of subsequent Q-wave MI at one year was highest in the PCI group (8.3%), lowest in the CABG group (2.0%), and intermediate in the medical therapy group (5.0%). Rates of event-free survival (freedom from cardiac death, MI, or refractory angina requiring revascularization) were significantly different (p < 0.0001) among the three

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See page 1743
groups; CABG event-free survival = 93%, medical therapy event-free survival = 88%, and PCI event-free survival = 76% (8). Freedom from angina at one year was significantly higher among CABG–treated patients (61%) compared with medically treated patients (36%), but was not significantly different from PCI–treated patients (55%), while the need for subsequent revascularization was significantly greater among those who underwent PCI compared with CABG or medically treated patients—with the need for repeat PCI being the major “driver.”

The MASS-II data are provocative and suggest strongly that a routine strategy of PCI for patients with mild-to-moderate angina and multivessel CAD patients is not superior to CABG surgery or medical therapy, and may be associated with lower rates of event-free survival. While PCI may be comparable to CABG surgery for angina relief, the MASS-II trial results suggest that PCI does not appear to be a “clear winner” with respect to reducing long-term (one year) clinical events in stable angina patients.

What is the relevance of the MASS-II trial to contemporary clinical practice? Fundamentally, there are two reasons to recommend PCI in angina patients: 1) for symptom relief, when medical therapy is ineffective; and 2) to improve prognosis. Importantly, for a significant percentage of angina patients, revascularization is not considered essential for either symptom relief or prognostic reasons. In fact, many patients with CAD do not have debilitating symptoms, and the data to support revascularization in these have undergone less rigorous study, yet there are many CAD patients without refractory or debilitating symptoms who lack the prognostic indicators mandating revascularization (i.e., objective evidence of inducible ischemia, LV dysfunction, and so on) (9). Despite this, millions of these patients are undergoing PCI/stenting all over the world while the evidence–based value of that approach has been sparse (9).

Why is this the case? Most probably, physician preference and societal expectation may play an important part—at least in the U.S. Many clinical and interventional cardiologists advocate prophylactic dilation of significant coronary stenoses irrespective of symptoms or compelling evidence of ischemia, in the belief that this reduces the risk of progression to coronary occlusion, prevents MI, or improves prognosis. Yet, published data—notably the recent seven-year outcomes data from the Randomised Intervention Treatment of Angina (RITA)-2 trial (10)—do not support this belief, because dilation of one or more coronary stenoses did not subsequently affect the incidence of MI or death over this long-term period of follow-up.

Nonetheless, many physicians approach CAD patient management based largely on angiographic findings and accept the premise that an “oculostenotic reflex” inevitably leads to an obligate “oculolatory reflex.” Moreover, as King (9) emphasizes, the corollary of this clinical practice is the impact it has on patient/family perception and decision-making; patients who are told they have a “blockage” often display an “auditory-stenotic reflex,” namely, “if it is blocked, I want it fixed.”

Finally, in comparing PCI with medical therapy, several small trials have compared PCI with various medical therapy strategies in stable angina patients with both single-vessel and multivessel CAD, but most have reported only limited follow-up data (10–12). Overall, compared with medical therapy, these trials show that PCI significantly improved angina relief and short-term exercise tolerance, but did not significantly reduce death, MI, or need for subsequent revascularization. In a meta-analysis of six RCTs (13) from 1979 to 1998, comprising 1,904 patients (Fig. 1), the only outcome measure that favored PCI compared with medical therapy was angina relief (odds ratio [OR] 0.70; 95% confidence interval [CI] 0.50 to 0.98). For the end points of death, MI, and need for repeat PCI, the ORs trended strongly in favor of medical therapy (29% to 42% better than PCI), while the need for subsequent CABG was almost 60% less likely among medically treated patients (13). However, except for this CABG comparison, the CIs surrounding the other point estimates were wide, owing to the relatively small sample sizes.

Clearly, such a meta-analysis (13) of underpowered studies cannot be considered in any way definitive, but unlike the prognostic advantage afforded by CABG surgery in many subsets of CAD patients with stable angina pectoris, there is no compelling evidence from among the more than 45 RCTs (13,14) to date that PCI with stenting is superior to standard balloon angioplasty, CABG surgery, or medical therapy with respect to reducing the “hard” end points of death or MI. For the end point of angina relief, PCI appears to be better than medical therapy and probably the same as CABG surgery. Thus, PCI appears to favorably affect quality of life only and not prognostically important event-free survival.

Therefore, treatment choice should be guided by symp-
tom status and severity. The majority of patients with mild-to-moderate angina can be safely managed medically, but PCI is appropriate if symptoms are not adequately controlled by medication or if other high-risk features are apparent.

Lastly, the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in almost 2,300 CAD patients may clarify further whether PCI combined with aggressive, multifaceted medical therapy is superior to intensive medical therapy alone on the long-term clinical events of death, MI, or troponin-positive acute coronary syndromes during a 2.5- to 7-year (average, 4.5 years) follow-up. The COURAGE trial seeks to advance the paradigm that the best clinical outcomes can be achieved by coupling PCI with intensive, guideline-driven medical therapy, and the hypothesis of COURAGE is that such a combined approach will be superior to a medical therapy-only strategy in patients with symptomatic multivessel CAD. Enrollment in the COURAGE trial has now concluded and follow-up is underway until at least mid-2006. Regardless of the clinical outcome, however, COURAGE promises to be an important, landmark trial that will shed much-needed light on elucidating the best therapeutic approach to managing millions of angina patients in the U.S. and worldwide, and it will add to the growing body of scientific studies, such as RITA-2 and MASS-II, in better defining treatment options—and perhaps the best “winning strategy”—for both patients and physicians.

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