Optimal Medical Therapy
Is a Proven Option for Chronic Stable Angina

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The authors of the meta-analysis of a percutaneous coronary intervention (PCI)-based invasive strategy for improving prognosis for the treatment of angina conclude that a pooling of data from various studies can be sufficiently powered to evaluate the impact of PCI on long-term mortality. However, most randomized coronary artery patient trials have insufficient power to detect significant differences in hard end points. Randomized trials in patients with chronic stable angina enroll few patients who are over age 65 years, have depressed ventricular function, have clinical instability, or who have undergone previous coronary artery bypass grafting (CABG) or PCI. “Medical therapy” today no longer means the absence of PCI, but rather the presence of intensive, evidence-based pharmacologic intervention. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) trial randomized 2,287 patients to optimal medical therapy alone or optimal medical therapy plus PCI. Optimal medical therapy consisted of antiplatelet therapy, anti-ischemic therapy, and aggressive lipid and blood pressure control. Based on the strength of the evidence, the author of this commentary recommends more-aggressive medical therapy for patients with moderate-to-severe angina, and PCI or CABG for many patients in whom symptoms persist.

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During the past 4 decades, there have been many improvements in our therapeutic options for patients with coronary artery disease. We have better cardiac surgical techniques, new and improved percutaneous coronary interventions (PCIs), and advances in the medical treatment of coronary atherosclerosis, including therapy for modifiable risk factors. Effective drugs that improve prognosis include antiplatelet agents, statins, beta blockers, and angiotensin-converting enzyme inhibitors (1–5).

Therapeutic Options Currently Available

According to the recommendations of the American College of Cardiology/American Heart Association clinical practice guidelines (4), the 3 major options for treating patients with coronary artery disease include medical therapy only, PCI, and coronary artery bypass grafting (CABG). Medical therapy is necessary whether or not revascularization is performed.

PCI

Percutaneous coronary intervention is indicated in patients with acute coronary syndromes in whom revascularization improves long-term prognosis (6–8). Percutaneous coronary intervention is the most popular revascularization procedure used to treat stable angina and angina equivalents; however, it may not be necessary for many patients with chronic stable coronary artery disease but no acute coronary syndromes. The impact of PCI on the long-term prognosis of these patients is still not well defined. Although drug-eluting and bare metal stents are highly effective in treating severe coronary stenoses, they do not treat atherosclerosis beyond the stenotic coronary segment in which they are implanted.

Randomized Clinical Trials of PCI Versus Medical Therapy

Patients with stable coronary artery disease have a very good long-term prognosis, and large sample sizes are required to separate potential differences in treatment regarding uncommon events. Most randomized coronary artery patient trials performed to date have insufficient power to predict hard end points (5). The recurring question about all randomized studies is whether or not the results can be generalized to less selective patient populations in practice settings. Randomized trials in patients with coronary artery disease have enrolled few patients who were over 65 years of age, had depressed left ventricular function, had clinical instability, or who had undergone previous CABG or PCI. Some trials have failed to define the medical therapy that
patients received or the success of risk factor control during the study. “Medical therapy” today no longer means the absence of PCI, but rather the presence of intensive, evidence-based pharmacologic and lifestyle interventions. The results of randomized trials do not necessarily apply to other populations that are not well represented because of the small number randomized.

The COURAGE Trial

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) trial randomized 2,287 patients to optimal medical therapy alone or optimal medical therapy plus PCI (3). There was objective evidence of ischemia and extensive angiographic disease as well as a high prevalence of comorbidity. Optimal medical therapy consisted of antiplatelet therapy, anti-ischemic therapy, and aggressive lipid and blood pressure control. The projected composite 3-year event rate was 21% in the optimal medical therapy group and 16.4% in the PCI group (relative difference: 22%) during a follow-up period of 2.5 to 7 years (3). The statistical analysis estimated that the enrollment of 2,270 patients would provide a power of 85% to detect the anticipated difference in the primary outcome at the 5% 2-sided level of significance (3). Estimates of the cumulative event rate were calculated by the Kaplan–Meier method (3). The primary efficacy of PCI as compared with optimal medical therapy was assessed by the stratified log-rank statistic (3).

The 4.6-year cumulative primary event rate was 19% in the PCI group and 18.6% in the medical therapy group (hazard ratio [HR] for the PCI group: 1.05, 95% confidence interval [CI]: 0.87 to 1.27; p = 0.620) (3). There were 85 deaths (7.6%) in the PCI group and 95 deaths (8.3%) in the medical therapy group (HR: 0.87, 95% CI: 0.65 to 1.16; p = 0.38). Although the degree of angina relief was significantly higher in the PCI group, there was also substantial improvement in the optimal medical therapy group. During the trial, 33% of the optimal medical therapy group crossed over to revascularization, but 67% did not. Many were asymptomatic on optimal medical therapy. These findings reinforce clinical practice guidelines (1), which state that PCI can be safely deferred in patients with stable angina.

In the COURAGE trial, more uniform data and consistent selection criteria were used than is possible in a meta-analysis. Only patients undergoing a prescribed diagnostic workup were randomized. An important lesson from the COURAGE trial is that therapeutic options should be reviewed with the patient with an emphasis on patient preference and quality of life because deferral of PCI did not carry a penalty in terms of survival or nonfatal myocardial infarction.

Meta-Analysis

Meta-analysis combines and summarizes available evidence quantitatively. Although it can be used to combine nonrandomized studies, meta-analysis is most valuable when used to summarize all the randomized trials addressing a particular therapeutic problem (9–11). Furthermore, the best meta-analyses obtain and analyze the raw patient-level data (9), rather than working with only what is available in the published forms of each trial. Ideally, meta-analysis permits the aggregation of lesser-powered studies into one analysis powered to detect a significant difference between treatments. Well-defined inclusion criteria relevant to the question to be asked and comprehensive accounting for all studies using these criteria are critical to the success of any meta-analysis addressing this issue. Importantly, not all published meta-analyses are reliable sources of evidence on a particular clinical problem. The method of analysis must be carefully examined to define proper study design and analysis (9). The results of a well-done meta-analysis are likely to be more meaningful if the analysis includes at least several large-scale, properly performed randomized trials.

Meta-analyses typically focus on summary measures of treatment benefit, such as odds ratios or relative risks. Clinicians should also consider what absolute risk reduction can be expected from the therapy.

Meta-Analysis of PCI

In this issue of the Journal, Schömig et al. (5) pooled together the results of 17 randomized trials comparing PCI and medical treatment as strategies in patients with stable angina and no acute coronary syndromes. The purpose of this meta-analysis was to evaluate whether PCI affects long-term survival of patients with stable coronary artery disease (5). The meta-analysis intended to include all studies that investigated the relative merit of PCI in patients with stable coronary artery disease and “symptoms or signs” of ischemia. Trials were accepted or excluded depending on whether specific relevant data were available. Intention-to-treat was the method of analysis. The number of patients included in the 17 trials ranged from 44 to 2,287 (the COURAGE trial).

The primary end point of the meta-analysis was all-cause death. Other outcomes of interest were cardiac-caused death and nonfatal myocardial infarction. The randomization follow-up ranged between 12 and 122 months (average 51 months). The analysis was performed according to the treatment group; 3,675 patients were assigned to the PCI-based treatment group and 3,838 to the medical treatment group. There was no significant difference across the trial regarding mortality. However, allocation to the PCI group was associated with a 20% reduction in the odds ratio of all-cause death (odds ratio: 0.08, 95% CI: 0.64 to 0.99). In addition, randomization to the PCI groups was associated
with a nonsignificant reduction in the odds ratio for cardiac death.

There are several important limitations to this study by Schömig et al. (5). The methods of diagnosing myocardial ischemia, the extent of coronary artery disease, and the presence of periprocedural or spontaneous myocardial infarction in individual patients and subgroups are not given. The odds ratios from mortality in individual trials with 95% confidence intervals are large. Patient-level data were not analyzed. Some studies included patients with recent myocardial infarction who were not clearly in a stable phase of their disease, threatening the generalizability of the findings to patients with stable coronary disease. There was a large variability in the comprehensiveness and intensity of secondary prevention provided to patients, calling into question the appropriateness of combining data from such different therapeutic regimens. Therefore, these findings using a meta-analysis instead of a large randomized controlled trial suggest but do not establish that the PCI-based invasive strategy may improve long-term survival compared with medical treatment strategy in stable coronary artery disease. The difference between the findings of the meta-analysis and the COURAGE trial may be attributable to a difference in the accuracy of the data being analyzed, with patient-level data from a large randomized controlled trial being superior. Furthermore, the distinctly aggressive and comprehensive anti-atherothrombotic medical therapy delivered in the COURAGE trial may also explain the difference.

Conclusions

The investigators of the meta-analysis conclude that a PCI-based invasive strategy may improve long-term survival in patients with stable coronary artery disease, and that this strategy may improve long-term survival compared with medical treatment strategy in stable coronary artery disease. The difference between the findings of the meta-analysis and the COURAGE trial may be attributable to a difference in the accuracy of the data being analyzed, with patient-level data from a large randomized controlled trial being superior. Furthermore, the distinctly aggressive and comprehensive anti-atherothrombotic medical therapy delivered in the COURAGE trial may also explain the difference.

Key Words: chronic stable angina • PCI • long-term follow-up • anti-anginal therapy • hard cardiovascular end points.

REFERENCES


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