How Do We Best Treat Patients With Ischemic Heart Disease?

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Despite investigations over several decades, it is still difficult to define an optimal treatment strategy for patients with ischemic heart disease. Some of the many reasons for this dilemma include delayed and highly variable symptomatic presentation, lack of a clear relationship between symptom severity and outcome, a changing population (aging and more women), changing therapies, and a relatively low overall event rate for patients in the chronic stable phase. The problem is placed into focus, however, when one considers that as the “baby boomers” age, we will see a marked increase in the prevalence of ischemic heart disease without a clear understanding of how aggressive we should be with our medical approach and whether expensive revascularization procedures offer clear benefit over the best medical approach.

The prevailing notion from past trials is that subgroups of patients with ischemic heart disease, principally those with anatomic findings suggesting the potential for severe ischemia (left main stenosis or severe multivessel disease with impaired left ventricular function), may do better with surgical revascularization than medical therapy. But these are only a small and select fraction of ischemic heart disease cases, and these results are dated by older technologies.

Yet, in patients who were asymptomatic or mildly symptomatic after infarction, 3 small randomized trials of CABG surgery versus medical therapy have shown no distinct benefit in favor of surgery. Norris et al addressed this issue in 100 consecutive patients believed to be at high risk because they had second or third infarctions. The majority had triple-vessel coronary artery disease, and most had depressed left ventricular function (ejection fraction <50%). Those with left main obstruction and severe symptoms were not included. Comparing those randomized to CABG with those receiving medical therapy, no differences in mortality or other important outcomes were found in 4.5 years (mean) of follow-up. These same investigators also terminated a similar randomized trial done in patients after first infarction, when no outcome trends were observed. Likewise, group C of the CASS (asymptomatic 3 weeks after infarction) included 160 patients randomized to either CABG or medical therapy. Again, no significant improvement was seen after CABG surgery compared with medical therapy.

Recent advances in medical therapy that definitely reduce death and myocardial infarction (eg, aspirin, β-blockade, HMG CoA reductase inhibition, and ACE inhibition after myocardial infarction) have raised questions. These medical treatments were not present in most of the early bypass versus medicine comparisons noted above. Likewise, recent trends toward more intense management of ischemia (2 or 3 drug combinations and higher doses) and treatment of associated conditions (eg, hyperlipidemia, diabetes, hormone replacement, and lifestyle modifications) have suggested that additional benefit may be obtained from more intense medical therapy. However, many others argue that surgery has also changed (use of more arterial grafts, more complete revascularization, minimally invasive approaches) and that these changes may yield better outcomes. Also, the medical therapies are likely to contribute to reducing event rates in patients undergoing surgery, but such notions remain to be proven.

Recently, the Danish Multicenter Randomized Study of Invasive Versus Conservative Treatment in Patients With Inducible Ischemia After Thrombolysis for Acute Myocardial Infarction (DANAMI) reported that revascularization (CABG or PTCA) reduced the frequency of reinfarction, unstable angina, and stable angina over 2.4 years of follow-up. But there was no significant difference in mortality, and the conservative treatment choice for anti-ischemic therapy was “according to local practice.” After 1 year in the conservative group, despite compelling evidence for benefit, only 17% were receiving ACE inhibitors and only 40% β-blockers. Other criticisms are that the age was truncated at 69 years, so these data are not necessarily applicable to the increasing numbers of elderly people we are seeing with myocardial infarction, and bicycle exercise tests are not frequently used in this country.

In this issue of Circulation, a small, provocative pilot study examined the effect of “intense” medical therapy compared with coronary angioplasty, both directed at suppressing ischemia in survivors of myocardial infarction. Although these patients were clinically stable, each had large ischemic perfusion defects, which have been shown in previous studies to define a subpopulation at high risk for recurrent events. Anti-ischemic medical therapy consisted of a combination of a β-blocker, nitrate, and heart rate–slowing calcium antagonist, titrated to maximally tolerated doses defined by heart rate–and blood pressure–lowering criteria unless limited by...
side effects. In addition, all patients received aspirin and lipid-lowering agents. In the revascularization group, angioplasty was applied to the infarct-related artery, as well as any other arteries with a significant stenosis that supplied an ischemic zone defined by the perfusion scan. In this group, anti-ischemic medications were used only to treat residual symptoms, whereas aspirin and lipid-lowering agents were administered according to the same guidelines as in the medical group. The authors observed that both revascularization and intense medical therapy reduced the size of the ischemic defect similarly. Although the number of events was small, clinical outcomes were similar in both groups. Furthermore, patients who remained clinically stable had a greater reduction in perfusion defect size than those who had a recurrent cardiac event. Although the numbers are small, this pilot provides very provocative data suggesting that suppression of ischemia, defined by radionuclide perfusion, can be achieved with intense medical therapy alone and that suppression of ischemia by either treatment can predict a better outcome.

Relative to questions of optimal treatment in ischemic heart disease, the recently reported 2-year results of the ACIP study published in Circulation also yielded intriguing data. For patients with ischemia during stress testing and daily life, death and nonfatal myocardial infarction were significantly reduced by early revascularization compared with patients assigned to an initial symptom-guided medical care strategy in which revascularization was reserved for clinical need. Of interest is that more aggressive anti-ischemic medical therapy (eg, ischemia-guided medical care strategy), although not as intense as in the pilot described by Dakik et al, provided a clinical outcome and ischemia suppression result that was intermediate between symptom-guided medical care and myocardial revascularization. At 2 years, the frequency of death or nonfatal myocardial infarction in this strategy, in which anti-ischemic drug therapy was titrated to suppress ischemia, was not significantly different from that with the early revascularization strategy, although the number of events was relatively small in all three treatment groups.

What do these findings suggest about the pathophysiology of ischemic heart disease and links with clinical events? Overall, these provocative data indicate that there is more to ischemic heart disease than an occlusive lesion in an epicardial coronary artery that may be suitable for revascularization. How does medical therapy result in improved myocardial perfusion? Indeed, the entire coronary vasculature, including the microcirculation, is probably involved. Large vessels with minimal lesions that are vulnerable to rupture, as well as endothelial dysfunction, a microvasculature with reduced flow reserve related to a variety of causes (coexistent hypertension, hypercholesterolemia, diabetes, etc), and other conditions (collateral development, status of myocardial metabolism, etc) are probably important. Although symptoms have proved to be unreliable as a management guide, residual ischemia, defined either by ECG abnormalities or by large perfusion defects, may be a clue to providing optimal treatment to affect the long-term course of ischemic heart disease.

However, in view of the limitations of the pilot-type trials outlined above (eg, short follow-up, small numbers of patients and events), larger and longer definitive prognostic trials are clearly required. To this end, the NHLBI is initiating SOCRATES (Study Of Coronary Revascularization And Therapeutic Evaluation$) in more than 6000 patients and the VA is initiating COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive drug Evaluation) in 3260 patients as definitive clinical trials to further define optimal therapy for patients with ischemic heart disease. Both trials plan to compare intense medical therapy with revascularization over the intermediate term (5 to 7 years). Although protocols have not been finalized, SOCRATES will contain a usual-medical-care reference group in which conservative symptom-guided care is applied and revascularization is deferred for unacceptable symptoms. The outcome in this group will be compared with that of the group treated with aggressive anti-ischemic drug therapy to suppress myocardial ischemia versus patients directly randomized to revascularization. This trial will test the hypothesis of control of ischemia by strategies controlling various levels of ischemia. The plan also provides for subrandomization among various specific medicines. Revascularization will include either CABG or PTCA. Conversely, SMART will have only 2 treatment groups: maximal medical therapy and angioplasty with or without stenting. When the data from these two trials become available, the clinician should have sufficient information to better manage the increasing numbers of patients with ischemic heart disease.

References

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