Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS-II)
Prologue to COURAGE

Spencer B. King III, MD

Clinical trials are organized for many different reasons. Most drug and device trials are designed to demonstrate the safety and efficacy of a drug or device, not to prove that they are the optimal treatments for patients. On the other hand, treatment strategy trials are designed to study the value of one therapeutic regimen compared with another when equipoise or confusion exists regarding which course to pursue. Assumptions are based on prior knowledge and opinion; in the case of coronary artery disease, most trials have been divided into those studying patients who “need” revascularization (ie, EAST [Emory Angioplasty versus Surgery Trial], BARI [Bypass Angioplasty Revascularization Investigation], RITA [Second Randomized Intervention Treatment of Angina], CABRI [Coronary Artery Bypass Revascularization Investigation], ARTS [Arterial Revascularization Therapies Study], SOS [Stent or Surgery], ERACI II [Estudio Randomizado Argentino de Angioplastia vs Cirugia II], and meta-analyses of these trials1,2) and those in whom medical therapy is judged to be a reasonable choice. The latter list is short—RITA-2 [Second Randomized Intervention Treatment of Angina]3 and the awaited COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation]4 and BARI 2D [Bypass Angioplasty Revascularization Investigation 2 Diabetes]5 trials.

Article p 1082

An assumption is made that patient groups can be identified that will be suitable candidates either for equipoise between 2 revascularization choices or for medical therapy versus revascularization. The study by Hueb et al6 in this issue of Circulation enrolled patients, most of whom would have been eligible for percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) trials, to 3 arms including medical therapy only. Eligible patients had multivessel coronary artery disease (3 vessels, 58%; 2 vessels, 42%), and the left anterior descending artery was involved in 92% of the patients. Therefore, these patients seem similar to those enrolled in prior trials of percutaneous transluminal coronary angioplasty versus CABG or the more contemporary stenting versus CABG, and yet the assigned groups were PCI, CABG, and medical therapy only.

Several questions are posed in this trial. In such patients, is 1 of the 2 revascularization strategies superior to the other? Is revascularization superior to medical therapy? Does any 1 of the 3 strategies emerge as the winner?

Individual trials and meta-analyses of trials have generated a generally held view that among patients enrolled with multivessel disease, surgery and PCI have comparable long-term hard end points of death or myocardial infarction (MI), but with more subsequent revascularization needed among patients randomized to PCI. Patients with diabetes are an exception to this consensus in that they fared better with surgery in the EAST and BARI trials,7,8 a finding that has not been refuted by subsequent studies; such patients are currently the focus of the ongoing FREEDOM [Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals with Diabetes],9 CARDIA [Coronary Artery Risk Development in Young Adults],10 and VA CARDS [Coronary Artery Revascularization in Diabetes]11 trials of patients with diabetes. These trials, including SYNTAX [TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries],12 which is not limited to diabetic patients, are all testing CABG against stenting with drug-eluting stents, which promise to markedly reduce the reintervention advantage of CABG but which, to date, have not been demonstrated to reduce death and MI.

Most of the therapeutic focus in recent years has been on advanced interventional technologies such as drug-eluting stents and improved surgical methods such as multiple arterial grafting, off-pump surgery, etc. It has been assumed that symptomatic patients, especially those with multivessel disease, deserve a revascularization procedure, and the only question is which one. The study by Hueb et al6 takes a broader look and assigns patients to 3 groups including medical therapy only. The results at 5 years point to an advantage of PCI over medical therapy in the end point for which PCI was originally developed: relief of angina. PCI patients compared with medically treated patients were more likely to be free from angina at 5 years (77% versus 55%). For all other end points, including death, MI, and subsequent revascularization, PCI had no advantage over medical therapy. One might say, “Yes, but they have less angina, and that is why the PCI was done.” Is this accurate? How many patients have interventions in which the only expectation is to reduce the use of nitroglycerin or to walk a bit faster? Most patients anticipate a better prognosis and might opt for an...
extended course of medical therapy if they believe they are not putting their life at excess risk.

Patients certainly would reject surgery as the initial strategy if they did not anticipate a better prognosis. Surgery provided better angina relief than medical therapy alone in the trial by Hueb et al \(^6\) (74% angina free versus 55%). Surgery also was associated with a nonsignificant advantage in survival (12.8% versus 16.2% for medical therapy only) and MI rates (8.3% versus 15.3%). Freedom from subsequent revascularization was significantly better for the surgical group than for the medical or PCI groups (3.5%, 24.2%, and 32.2%, respectively). The primary end point of the trial—death, Q-wave MI, or angina requiring revascularization—occurred significantly less in the surgical group (21.2%) than in the medical treatment group (32.7%) or the PCI group (36%). The informed patient might weigh the apparent protective effect of surgery against the inconvenience, discomfort, and immediate risk associated with that procedure. The results of this study are consistent with other studies that have predominantly used stenting compared with surgery. The death, MI, and reintervention rates in the PCI groups in the ARTS\(^6\) and SOS\(^14\) trials are not dissimilar. At 5 years’ follow-up, ARTS\(^13\) showed no difference in survival, but the surgery group survival rate in SOS was higher than that in the PCI group.\(^14\) Reintervention at 5 years in the PCI patients in this study\(^6\) (32.2%) is comparable with that seen in the other stent trials.

This trial found that freedom from the primary end point (death, Q-wave MI, and revascularization) was not better for PCI than for continued medical therapy, and surgery was superior to both of the other 2 strategies. How does this finding jibe with current clinical practice? The introduction to the current report\(^6\) states that the “study was designed to compare the relative efficacy of CABG with that of PCI or medical therapy in patients with symptomatic multivessel coronary artery disease requiring revascularization.” This is the state of “common wisdom” in the clinical approach to such patients. It may be a Freudian slip to state that patients with symptomatic multivessel disease “require revascularization,” but that is what is commonly done. Should physicians and patients accept these findings and, even though they require revascularization, opt instead for medical therapy unless they want to accept the costs and discomfort of CABG to gain the benefit of freedom from the triple primary end point?

The argument usually goes like this:

1. There is advanced coronary artery disease.
2. Revascularization is required to improve prognosis.
3. PCI is less invasive (ie, safer) and, therefore, should be selected.

The study by Hueb et al\(^6\) suggests:

1. There is advanced coronary artery disease.
2. Revascularization may not be needed to improve prognosis.
3. If it is, then CABG is the only therapy that will improve prognosis.

What is wrong with these conclusions? Nothing was wrong in the data presented except for the small size of the trial. The enrollment was not highly restrictive; 29% of those eligible were enrolled. Revascularization was more complete in the surgical group (3.3 vessels bypassed—all lesions bypassed in 74%) than in the PCI group (2.1 vessels dilated—complete revascularization in 41%). However, this is a fact of multivessel PCI. The New York State Registry has shown that two thirds of multivessel patients had incomplete revascularization by PCI.\(^16\) Not all patients received stents (72% stented; 62% with 2 to 3 stents; 11% with 1 stent). Although stenting is now more prevalent, it is not proven that more complete stenting would influence the hard end point of death or MI.

The main problem with the obvious conclusion of the 5-year follow-up of this study\(^6\) rests with the 5 years themselves. Technology has progressed rapidly, and now the availability and extensive use of drug-eluting stents challenges the prior data. Drug-eluting stents have certainly reduced the repeat revascularization rate among patients receiving stents, but the magnitude of this reduction has been exaggerated in the pivotal trials that required an angiogram at follow-up. Observation from a large database of patients receiving bare-metal stents shows a 1-year reintervention rate well below 10%.\(^17\) The number of reinterventions avoided per 100 patients with drug-eluting stents has been estimated to be about 5. The comparison of drug-eluting stenting in multivessel disease patients versus previous bare-metal stenting is, however, very encouraging. Although ARTS II\(^18\) was an uncontrolled registry, the 1-year results using drug-eluting stents show dramatic improvements compared with the stent arm of the ARTS trial. In fact, the results are comparable with those of the CABG group of ARTS. Some of the improvements are direct results of the drug-eluting stent, such as the reduced reintervention rates, and others, such as the 30-day reduction in death, MI, and urgent reintervention, are more likely attributable to improved antithrombotic therapy and improved technical skills. Whether these improvements will level the playing field between PCI and CABG will be examined in the SYNTAX and FREEDOM trials, which are currently underway. Follow-up for 5 years will be necessary to understand whether PCI can provide the same protective advantage that CABG has demonstrated in the past.

The other question raised by the study\(^6\) is whether revascularization is needed for all patients requiring revascularization. Patients enrolled in the COURAGE trial may have slightly less acuity than those in MASS [Medicine, Angioplasty, or Surgery Study], but this study will have a major influence on the attitude toward revascularization in patients who can be managed medically. The first report of COURAGE will be presented at the 2007 American College of Cardiology Scientific Sessions. If PCI does not improve outcomes in these patients receiving optimal medical therapy, then some physicians will have the courage to avoid revascularization for their patients. On the other hand, a significant benefit for PCI would reinforce current clinical practice patterns. In another year, BARI 2D will begin providing similar information on diabetic patients with coronary artery disease.
It is hoped that the findings of MASS will focus therapeutic selection choices on the multiple options that are available. Optimal outcomes, regardless of revascularization, require optimal secondary preventive therapy, which is evolving at a pace to rival that of interventional devices. Despite the important contributions of these trials to our understanding of how to manage patients, it is clear that trials are not enough. Within every trial reside patients with unique characteristics and needs. Clear-headed judgment, albeit informed by trials, is required when recommending the strategy with the greatest chance of success.

Although the trial by Hueb et al is small and, perhaps, only hypothesis generating, it challenges some common wisdom and is an appropriate prologue to the larger trial results that will be coming soon.

Disclosures
Dr King is a consultant for Medtronic, Inc, and has received support from Cordis Corporation, Sanofi-Aventis, and Bristol-Myers Squibb.

References

KEY WORDS: Editorials ■ coronary artery bypass grafting ■ therapy ■ coronary disease
Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS-II): Prologue to COURAGE
Spencer B. King III

Circulation. 2007;115:1064-1066
doi: 10.1161/CIRCULATIONAHA.106.675454
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/9/1064

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click RequestPermissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and RightsQuestion and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/