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Editorial

Is Optimal Medical Therapy "Optimal Therapy" for Multivessel Coronary Artery Disease?

Optimal Management of Multivessel Coronary Artery Disease

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When treating patients with coronary artery disease (CAD), clinicians consider whether management should be medical therapy (MT) alone or in addition to coronary revascularization. When revascularization is recommended, both coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) are potential options. Typically, the treatment recommendation is based on clinical presentation, severity and magnitude of ischemia, extent and distribution of coronary anatomic disease, presence of other noncardiac medical conditions, and evidence of the effectiveness of each strategy.

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Recognizing the substantial differences and implications between an invasive and noninvasive approach, clinical investigators have conducted large-scale clinical trials to assess and compare MT to revascularization and CABG to PCI. The clinical applicability of such studies, however, may be limited by several factors. Firstly, enrollment in "strategy trials" is typically difficult and prolonged, and initially declared sample target endpoints are rarely achieved. Secondly, given the slowly progressive course of stable CAD, outcomes need to be assessed over a long period, thus delaying the answers to the proposed research questions. In addition, as both revascularization approaches and medical therapies evolve and become more refined over time, it may often be difficult to interpret study findings in the context of these "moving therapeutic targets." A third concern relates to the types of patients enrolled in these studies and whether participating patients are truly reflective of those theoretically eligible. For example, some believe that once coronary anatomy has been defined in a patient with CAD and a judgment is rendered as to the suitability and appropriateness of revascularization, a treatment bias may significantly affect the decision as to whether or not a patient will be enrolled in a trial where treatment will be determined by random assignment. Despite these limitations and concerns, clinicians greatly value evidence derived from clinical trials comparing therapies for CAD. Indeed, such investigations form the basis for clinical practice guidelines and evidence-based care.

Patients with CAD represent a heterogeneous group, both anatomically and clinically; symptoms can range from sudden death to no symptoms whatsoever. For certain anatomic and clinical subsets, trials have provided solid evidence to guide decisions about therapeutic options. For example, in patients with acute myocardial infarction (MI) and cardiogenic shock, trial data demonstrate an overwhelming superiority of an initial invasive/revascularization strategy, as compared with MT alone. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial investigators found an absolute risk reduction in mortality of about 20% when patients were taken directly to the catheterization laboratory with a goal of immediate revascularization.[1] This study also reinforces the general tenet that the more advanced the anatomic CAD, symptom severity, and hemodynamic impairment, the greater the value of revascularization. The converse is also true, namely that in patients with limited CAD, normal left ventricular function and absent or minimal symptoms, rates of adverse cardiac events are low, and hence, revascularization provides little or no incremental value of improving prognosis in comparison to MT alone.

One subset of stable patients with CAD for whom questions remain is the group with multivessel disease, particularly if proximal stenosis of the left anterior descending coronary artery is present. The first large clinical investigation that compared MT to CABG, the Veterans Administration Cooperative Study, included such patients.[2] PCI had not been developed at that time. This trial provided the first evidence that CABG can improve survival in highly-selected patients with CAD, particularly those with left main CAD, although the actual number of such patients in the study was small (n=91). The Coronary Artery Surgical Study found that patients with 3-vessel CAD and impaired left ventricular function (ejection fraction <50%) benefited from CABG, a finding confirmed by the European Coronary Surgical study.[3,4] Once the value of CABG for selected patients with multivessel disease was acknowledged, most subsequent investigations addressed the question of whether PCI was an acceptable alternative to CABG. Ten trials have compared CABG to PCI in stable patients with CAD with multivessel disease. For these trials, PCI was performed with just balloon angioplasty or with bare metal stents. A recently published meta-analysis indicated no benefit of CABG over PCI in regards to the likelihood of death or MI.[5] Similar findings

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were noted when only those studies with at least 5-years of follow-up were analyzed.[6]

Of the clinical trials included in these meta-analyses, the second Medicine, Angioplasty, or Surgery Study (MASS-II) was particularly unique in that it was a three-armed trial that included a randomization to MT alone. At a single center, 611 patients were assigned to CABG (n=203), PCI (n=205), or MT (n=203). In this issue of *Circulation,* Hueb and coworkers report the study's findings at late follow-up that ranged from 9 to 15 years (11.4 years average).[7] The trial's primary end point was a composite of total mortality, Q-wave MI, and refractory angina requiring revascularization. The primary end point was observed frequently in all 3 groups: 33.0%, 42.4%, and 59.1% for patients assigned to CABG, PCI, and MT, respectively, with the lowest rate in the CABG group and the highest rate in the MT group. A similar pattern was observed for the individual endpoints of total death, cardiac death, and MI, with the distribution of rates for cardiac death and MI achieving significance. Further analysis demonstrated a "protective effect" of CABG over both PCI and MT for the composite end point. Of note, there was a strong trend for a similar effect of PCI over MT for the composite end point (heart rate 1.27 (0.99 to 1.62), with a probability value (0.06) that nearly achieved nominal significance.

Although the rates for total death were not significantly different among treatment groups, the observed rates for CABG and PCI were almost equal (25.1% and 24.1%, respectively), while mortality was numerically higher in the MT group (31.0%). As expected, the rate of subsequent revascularization was lowest among patients with CABG (<10%) and similar (about 40%) in patients with PCI and MT. Stroke was relatively infrequent but appeared highest among patients with CABG (8.4%). Individual clinical factors associated with increased mortality included age, presence of diabetes mellitus, and systemic hypertension. These same factors were also associated with an increased rate of cardiac death as was assignment to MT as compared to CABG. Such a relationship was not observed between PCI and CABG or PCI and MT.

Certain findings from this 10-year follow-up report were similar to those reported at 5 years.[8] For example, at both intervals the composite end point favored CABG, primarily due to differences in rates of subsequent revascularization. In addition, no difference across treatments for total mortality was noted at either time point. At 10 years, however, there were differential rates of cardiac death and MI among the 3 groups. No significant differences were observed at 5-years of follow-up (although trends were present) whereas at 10-years, CABG was significantly associated with a lower risk for cardiac death than MT and a lower risk for MI than either MT or PCI. Moreover, analysis of prespecified subgroups demonstrated a clinical benefit in terms of the primary composite end point of PCI over MT for women, patients <65 years, and those with systemic hypertension. No subgroups were identified that demonstrated superiority of MT over either CABG or PCI. To summarize, the 10-year results of MASS-II indicate that revascularization, particularly with CABG, improves the outcomes of patients with multivessel disease in comparison to MT alone. These clinical benefits are substantial in favorably impacting prognostically-important events such cardiac death and MI, and not just the need for subsequent revascularization procedures.

We should acknowledge certain shortcomings of MASS-II before simply "accepting" these results. Firstly, the number of patients in each study group was small, about 200 each. Small sample size limits the precision of observed event rates. Secondly, as in any trial of this type, blinding is difficult such that biases could influence endpoints such as angina or the indication for a subsequent revascularization procedure. Thirdly, patients were enrolled at a single center and the nature of treatments rendered may differ elsewhere. Finally, MT may not have been as intensive as currently possible. On the other hand, a major strength of the study was the completeness of follow up that was 100% for vital status, a particularly important feature of a trial when differences in survival were observed.

The implications of the 10-year findings from MASS-II are substantial. To this point in time, data from individual clinical trials have not demonstrated any benefit from revascularization by CABG or PCI over MT alone in regard to decreasing the incidence of death (total or cardiac) or MI. In fact, recommendations of appropriateness and guideline documents have emphasized the lack of clinical benefit and have advocated against the routine application of revascularization procedures for patients with multivessel disease and preserved left ventricular function, except for relief of symptoms unresponsive to aggressive medical therapy. The recently completed Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial forms much of the basis for such a position.[9] In this large, multi-national investigation, an initial management strategy of PCI combined with intensive "optimal" MT was compared to a strategy of deferred PCI and "optimal" MT. At 5 years, COURAGE investigators found no difference in rates of death, MI, stroke, or hospitalization for an acute coronary syndrome between the two treatment groups. COURAGE patients differed, however, from MASS-II patients in that nearly one third of COURAGE patients had single vessel disease (there were none in MASS-II) and only about one third had proximal left anterior descending involvement (92% in MASS-II). The extent of CAD, therefore, was substantially greater in MASS-II patients than those in COURAGE, a possible explanation for the differences in findings. Of note, COURAGE did observe a benefit for PCI over MT for relief of angina. A similar effect was seen for CABG in MASS-II. Importantly, MASS-II also compared revascularization by CABG to that of PCI. Although significant differences in outcome were not uniformly demonstrated, event rates for most endpoints (except stroke) were lower for CABG. As noted above, however, cardiovascular therapies evolve and become more refined over time. Although MT, CABG, and PCI have each improved, PCI has arguably changed the most in terms of procedural technique, intensive use of ancillary antiplatelet and anticoagulant drugs, and stents with superior design features, including thinner struts and antirestenotic drug delivery.

The Synergy between PCI with Taxus and cardiac Surgery trial compared CABG to PCI in patients with multivessel

CAD that was more anatomically complex than that of those enrolled in MASS-II.[10] With follow up now extending to beyond 2 years, no differences in death or MI have been observed between groups. CABG was superior in regards to the need for subsequent revascularization procedures but, on the other hand, it was associated with a small but statistically significant excess incidence of stroke. Given these considerations, and until such evidence-based trials data are available, clinicians might be justified in anticipating that current-day PCI may provide results more similar to those achieved from CABG in MASS-II.

Finally, little data exist from randomized trials to guide decision making in patients with multivessel disease who have moderate-severe myocardial ischemia on noninvasive testing and minimal or no symptoms. Such patients seem to be at high risk for cardiovascular events and accordingly would be expected to benefit from revascularization strategies applied to reduce or relieve ischemia. The MASS-II protocol included a baseline and annual exercise stress test for each patient. Unfortunately, the incidence and extent of ischemia as related to treatment strategy and to clinical outcome was not described. Clearly, this relationship between ischemia, treatment approach, and outcome is one that is worthy of further investigation.

Disclosures

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