EDITORIAL

Why We Still Need Randomized Trials to Compare Effectiveness

Laura Mauri, M.D.

Over the past 20 years, there have been 12 randomized trials in which the revascularization strategies of coronary-artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have been compared, against the background of advances in both fields. Percutaneous treatment of multiple vessels has become more feasible, more durable, and more common, and yet the most contemporary randomized trial comparing PCI with CABG showed that CABG remained the preferred strategy for the treatment of patients with three-vessel coronary artery disease, owing primarily to a greater need for second procedures after PCI.[1]

Weintraub and colleagues[2] now present the results of the American College of Cardiology Foundation (ACCF) and the Society of Thoracic Surgeons (STS) Database Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) study, a nonrandomized comparison of patients who underwent PCI or CABG for the treatment of two-vessel or three-vessel coronary artery disease. The strengths of these data are the breadth and number of patients included — more than 180,000 from the combined ACCF[3] and STS[4] databases. This report is the most comprehensive sample to date of revascularization outcomes in U.S. patients 65 years of age or older. Although no difference was evident at 1 year, the adjusted all-cause mortality at 4 years was lower by 4.4 percentage points with CABG than with PCI.

The validity of these findings rests largely on a determination of whether adequate control for confounding was possible. Inclusion of patient data in procedural data sets is voluntary, and auditing is limited.[3,4] Follow-up data were obtained with the use of an algorithm that matched the registry data to administrative data. As might be expected in a nonrandomized cohort, patients in the two treatment groups differed significantly with respect to age, sex, coexisting conditions, and urgency of treatment. Propensity scores (which were used to estimate the probability, on the basis of patient and hospital characteristics, that patients would be selected for CABG) were also quite divergent, indicating a strong selection bias. Even with the findings adjusted for propensity score, the authors state their conclusions cautiously, and they acknowledge the possibility of residual confounding.

Selection bias is inherent in a cardiologist's decision about which invasive procedure to recommend for a patient. The divergence of the propensity scores in this study confirms what might be expected, which is that physicians are indeed choosing patients with divergent clinical profiles for the two procedures, and this makes any method of adjustment problematic. Furthermore, some factors that might influence the treatment selection could not be assessed with the available data, and many of these factors also have strong relationships to mortality. The feasibility of the procedure for a particular patient, the burden of coronary atherosclerosis (diffuse vs. focal disease), the patient's degree of frailty, the likelihood of adherence to treatment, and the patient's preference are examples of factors that influence both treatment and

outcome. Because these factors were not assessed or adjusted for, an imbalance in any factor, alone or in combination, could explain the difference in mortality that was observed. The authors provide a careful analysis to attempt to quantify the effect of a hypothetical confounding variable on their findings, but, of course, without specific data, one can only make assumptions about which factors or combinations of factors might have such an effect.

Some randomized studies have shown lower mortality with CABG than with PCI in specific subgroups. Among patients with diabetes in the Bypass Angioplasty Revascularization Intervention trial (BARI; ClinicalTrials.gov number, NCT00000462), cardiac mortality was lower in the CABG group than in the PCI group at 10 years of follow-up.[5] This benefit appeared to be attributable to patients with the most extensive disease.[6] In the most contemporary study, the Synergy between PCI with Taxus and Cardiac Surgery trial (SYNTAX, NCT00114972), there was no significant difference in mortality in the overall cohort, but in the subgroup of patients with three-vessel disease, mortality was lower by 3.2 percentage points in the CABG group than in the PCI group at 3 years.[7] It is plausible that, in patients with diffuse atherosclerosis, CABG reduces the risk of fatal myocardial infarction more effectively than does focal treatment.[8,9]

A mortality benefit attributable to CABG has not been evident, however, among patients with two-vessel disease or among patients with three-vessel disease with focal lesions (SYNTAX score of <23, on a scale of 0 to 70, with higher scores indicating more complex disease).[7] Among patients with a relatively low burden of coronary atherosclerosis, the early risk of stroke[1] may outweigh the potential for late mortality benefit from CABG. Furthermore, modern PCI strategies, which have yet to be compared with CABG, favor the use of focal treatment only for vessels that are associated with ischemia, rather than an all-or-none approach.[10] In the context of the results of randomized trials, a difference in mortality between PCI and CABG was expected among patients with complex disease, but it was not expected among patients with a lesser atherosclerotic burden. Differences in unrecorded selection factors that relate to prognosis, rather than an intrinsic mortality benefit from CABG, may explain why the results in lower-risk patients in the study are not consistent with the results from randomized trials.

If observational registries require randomized trials to explain their results, what is their value in comparing treatment strategies? Patients who consent to participate in the controlled framework of a randomized study are systematically different from those who do not,[11,12] and unselected registries are the only way to examine the generalizability of results from randomized trials. Observational studies provide detail on how and in whom treatments are being performed and how patient selection varies between treatments, but there is no substitute for randomized trials to eliminate selection bias between treatments. The two approaches are thus complementary. Observational studies allow clinical research to represent the full breadth of treated patients and offer tremendous power — especially as data are collected and analyzed with greater rigor. However, we must also continue to give priority to randomized trials on the most salient questions regarding treatment strategy and to simplify their design and conduct to be more inclusive and efficient.

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From the Division of Cardiovascular Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston.

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