EDITORIAL COMMENT

Present-Day PTCR Versus CABG: A Randomized Comparison With a Different Focus and a New Result*

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Within the past decade seven randomized controlled trials have been published comparing percutaneous transluminal coronary angioplasty (PTCA) to coronary artery bypass graft surgery (CABG) (1–7). The mortality rates and important clinical outcomes during follow-up periods ranging from one to five years varied slightly, but essentially each study has shown that the mortality rates between the two revascularization techniques are not significantly different. However, patients randomly assigned to CABG universally have a lower incidence of angina and less need for repeat procedures during follow-up.

With one exception (3) all the trials required the study population to include symptomatic patients with multivessel disease (MVD) and who were suitable candidates for both CABG and PTCA. Specifically excluded were patients with extensive coronary disease unsuitable for PTCA and those with poor left ventricular function. Most of the studies also excluded, per protocol, patients who had prior CABG or PTCA and those with very recent acute myocardial infarction (AMI). As a consequence, the resulting “MVD population” included in these trials was decidedly lower risk than the conventional MVD population for whom CABG is usually recommended.

The importance of this consideration has been demonstrated in two observational studies that have utilized large databases to compare PTCA and CABG (8,9). The New York State database included information on more than 60,000 patients from 33 institutions followed for three years undergoing either PTCA or CABG in New York (8). The Duke database included approximately 6,000 patients undergoing either procedure at that single institution (9). Both databases include the detailed clinical and angiographic data required to make proper risk adjustments on all patients. This is considered essential in forming valid comparisons among nonrandomized populations. The detailed angiographic data permitted the investigators to categorize patients beyond the conventional, but simplistic, one-, two-, and three-vessel disease classification and further stratify patients according to whether the lesions were proximal or distal in each of the major epicardial arteries. Both of these reports clearly demonstrate that survivorship is superior in patients undergoing CABG compared to PTCA in six of the nine subsets of patients stratified according to lesions in the proximal segments of the coronary arterial tree or involvement of the left anterior descending artery. These findings are consistent with those of Ringqvist et al. (10) in seminal studies on the natural history of coronary artery disease patients performed during the Coronary Artery Surgery Study (CASS).

Based on these considerations the cardiology community currently functions with an evidence-based mind-set that, for patients with severe extensive coronary artery disease, CABG is the preferred method of revascularization. However, for patients with less extensive multivessel disease who could be treated successfully by either CABG or PTCA there are practical reasons to consider PTCA as the more “patient-friendly approach.” This is particularly true if both the physician and patient accept the strategy of including repeat PTCA as part of the “price to be paid” for selecting the less invasive technique.

In this issue of the Journal, Rodriguez et al. (11) present the first data from a randomized comparison of present-day PTCR (coronary angioplasty with stenting) versus CABG, indicating an improved outcome with PTCR. The primary end point of this study from South America is the 30-day incidence of major adverse cardiac events (MACE: death, Q-wave myocardial infarction, stroke, and repeat revascularization procedures). The incidence for PTCR was 3.6% and for CABG 12.3% (p = 0.002). Driving this combined end point was the 30-day surgical mortality of 5.7% and a Q-wave MI rate of the same magnitude (5.7%) when compared to a PTCR mortality rate of 0.9% and a Q-wave MI rate of 0.9% (p = 0.013%). At one-year follow-up, survival was 96.9% in the PTCR group and 92.5% in the CABG group (p = 0.017). As the Kaplan-Meier survival curves demonstrate, the excess deaths among the surgically assigned patients were confined to the first 30 days of follow-up and after that the numbers of patients dying were the same in each group. The same is true of the MI curves. The study further reports that the need for repeat revascularization procedures, while higher in the PTCR group (16.8% vs. 4.8%, p = 0.002), is substantially lower than the need reported in earlier studies with conventional balloon angioplasty (30% to 40%).

For many reasons, this report is certain to polarize any readership interested in coronary revascularization into those who applaud the work and those who condemn it. The opponents are certain to criticize 30-day MACE as a meaningless primary end point. It is widely recognized that

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undertaking an intervention as major as CABG carries an inherent procedural risk of mortality, Q-wave infarction, and stroke that outweighs the comparable risks of the less invasive procedure of conventional PTCA. Considering existing data, the deployment of stents at the time of PTCA not only decreases the incidence of restenosis but lessens the occurrence of abrupt vessel closure and early reclosure that should further widen the gap of early morbidity and mortality (12). These physicians will claim the primary end point was selected in a preordained fashion to gain statistical significance of PTCR over CABG but fails to address the basic question of which strategy is better in the longer run.

Proponents of the study will agree with the investigators' opening sentence: "previous randomized studies comparing balloon angioplasty vs. CABG have demonstrated equivalent safety results." Even though none of the previous randomized comparisons was powered to examine early mortality or complication rates, the largest of these trials, BARI, showed a significantly higher incidence of inhospital Q-wave infarction, respiratory failure, reoperation for bleeding and wound dehiscence/infection in the CABG arm compared to PTCA (7). Among the latter group, however, both emergency and nonemergency CABG as well as emergency and nonemergency PTCA were significantly higher. In contrast, no statistically significant differences existed in either the cumulative survival curves or survival free of Q-wave myocardial infarction between the two groups over five years of follow-up (7).

Thus, members of the ERACI II study group could justify their contention that, if there is no long-term difference in these two outcomes in patients with symptomatic multivessel disease who were judged eligible for either procedure, it is important to examine which is the safer procedure. Accordingly, they properly sized their study population on "the assumption that either death, MI, repeat procedures and stroke would occur during hospitalization in 10% to 12% of patients assigned to CABG and in keeping with recent PTCR experience, in 3% to 4% of patients assigned to PTCA." This provided a power of 0.9 and an alpha error of 0.05. Although they give no details on how or who will accomplish it, the investigators planned a one-, three-, and five-year follow-up to study the secondary end points of anginal status, completeness of revascularization, and costs. Curiously, not stated (but eventually reported) was the need for repeat revascularization procedures in this industry-sponsored stent study.

The seemingly excessively high operative mortality (OM) rate of 5.7% in the ERACI II study (11) will also be the focus of much criticism. This, however, seems misplaced because with a small sample size of 450 patients and only 15 total deaths, the confidence intervals of the point estimate are extremely wide and renders the 5.7% figure quite imprecise. It is similar, however, to the 4.7% mortality rate reported in the earlier randomized comparison presented by these investigators in their very underpowered ERACI I study (2). It also falls within the range of other studies selected mostly from South America but also includes the VANQWISH trial from North America (13,14). The OM rate is nearly fivefold what it was in BARI, EAST, and CABRI, but the investigators maintain the 91% unstable angina rate and the 22% incidence of peripheral vascular disease rendered their population an unusually high-risk group for undergoing CABG. Unfortunately, the annual overall mortality rates for CABG at the individual participating sites in the ERACI II study (11) are not given and the reader remains unable to judge the validity of this claim.

To their credit, the researchers did explore the operative mortality of the surgically randomized patients stratified according to chronic stable angina, unstable angina class II, and unstable angina class III+C. Although the sample sizes of each group were too small for robust statistical analysis, an internal consistency showed a trend toward a greater in-hospital mortality as the severity of unstable angina worsened. We also know that, of the 1,076 patients who qualified for randomization in this trial, 27% underwent CABG outside the randomized study and their 30-day mortality rate was 5.1% with a 5.2% Q-wave AMI rate. It would be equally enlightening to know the operative mortality of the 287 patients in the registry who did not qualify for randomization but did undergo CABG. Left main disease was present in 27%, an equal percentage had poor left ventricular function, and 28% had multivessel disease too extensive to be managed by PTCA. One would anticipate an even higher OM rate in such a group.

It has been suggested that the large observational databases that contain relevant revascularization data be used to supplement information available from smaller-sized randomized trials (8). During the 1996 to 1998 time frame of ERACI II, more than 58,000 patients underwent CABG, and approximately 88,000 underwent PTCA in New York State, with all data entered into their respective Cardiac Surgery and Angioplasty Registry files. Unstable angina was present in 27,589 patients undergoing CABG and their OM rate was 3.3%, which is two and a half times greater than the OM rate for the approximately 31,000 patients operated on without unstable angina.

Similarly, of the 40,000 patients with unstable angina undergoing PTCA, the in-hospital mortality was 1.5%, which is threefold higher than the mortality in 48,000 patients undergoing PTCA without unstable angina. It thus seems valid to state that clinically unstable angina triples the procedural risk. At the same time, it is to be noted that the OM in the extremely large New York State unstable angina population was half that of the present study even though 56% of the patients were over 65 years of age and 27% of the population had peripheral vascular disease. Thus, the incidence of these two risk factors in the New York State population was significantly higher than in the South American patients enrolled in ERACI II.

The major strengths of the ERACI II study are its extensive use of stents (315 deployed in 225 patients assigned to PTCA) and its randomized design intended to
offset patient selection bias and distribute measured and unmeasured variables equally between the two study arms. Randomization, however, does not guarantee a flawless study, as is evidenced by the ascertainment bias that appears to exist in this trial. The unequal length of time between randomization to assigned treatment (9 days) and the substantially longer hospital stay of the CABG arm (4.1 days) would be expected to increase detected events in the CABG arm. The Q-wave MI would be the important variable most likely to be influenced by these disparities because MI was “judged to be present on the basis of a review of all electrocardiograms obtained.” Similarly, because it is unlikely that all patients in both arms underwent the protocol-specified dipyridamole thallium scintigraphy within 30 days, it is reasonable to ask: How were the missing data handled, and was the percentage of subjects studied the same in each arm? The follow-up data presented in the study are of very little use for two reasons. First, as is obvious from an inspection of Figures 3 and 4 (despite the expanded scale of the abscissa for the first 3 months), the death and MI rates are identical after 30 days, indicating that their excess during the first 30 days was procedure related. Second, the coiled stent chosen for this study was unfortunate because it has subsequently been shown to have one of the highest restenosis rates of all the stent devices. Additionally, it seems most inappropriate to undertake a comparison of the incidence of death and nonfatal MI during the 18-month follow-up period in this study with the 36-month follow-up period in EAST or the 12-month follow-up period in GABI (4,5).

Germane to this study, which “hypothesized that stent use might significantly decrease early complications in comparison to coronary bypass surgery,” is a very recent report by Hannan et al. (15) that compared both short- and long-term outcomes between balloon angioplasty and coronary stent placement from the New York State database. This study found that risk-adjusted in-patient mortality rates for PTCA and stent placement were not statistically different; however, patients undergoing angioplasty were, on average, significantly more likely to die at any point during the two-year period after the index procedure than were patients undergoing stent placement (relative risk 1.36, p = 0.003). The risk-adjusted in-patient CABG rate for patients undergoing PTCA was also significantly higher (2.72% vs. 1.66%, p < 0.001).

It would thus appear that the stage is set to undertake studies that compare stent placement with CABG as a function of both the number of vessels with disease and the specific location of the disease within the vessel. The ERACI II study further suggests to this reader that we would be wise to compare stent placement with modern medical treatment especially in the case of patients with unstable angina. It is challenging to speculate what the 30-day outcome would have been had this stent-placement study been compared to medical therapy that included glycoprotein IIb/IIIa inhibitors, low molecular weight heparin and clopidogrel for the 90% of the study population who had unstable angina. This might just be the study that has provided our first meaningful glimpse into the merits of delaying coronary artery intervention for as much as 30 days in patients with acute coronary syndromes.

Although I view their present study (11) as flawed, the ERACI investigators made important contributions to our search for improving coronary revascularization techniques, especially by underscoring the need to examine both the early and late outcomes of our therapeutic options. This will become ever more important as we approach the 10-year (plus) point of follow-up in many of the randomized trials. Clearly, when long-term event curves cross, the indication is that one of the procedures is preferable up to that point and the other is preferable thereafter. Such considerations give added meaning to the visionary words of the late Rene Favaloro, who claimed from the very outset: “The two techniques will always be complementary” (16).

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REFERENCES


