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EDITORIAL COMMENT

Did We Enjoy the Debate But Forget the Patient?

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The number of percutaneous coronary revascularization procedures performed has skyrocketed in recent years. The rationale for this acceleration has been the rapid and sustained relief of angina with percutaneous coronary revascularization and its ease of delivery relative to surgery. Although it is clear that for the majority of patients percutaneous and surgical revascularization therapies serve mainly as a symptomatic treatment, physicians and patients, consciously or subconsciously, tend to give lesser value to potentially more important disease-modifying therapies. In patients with coronary artery disease (CAD), these disease-modifying treatments include pharmacologic interventions such as lipid-lowering agents, antiplatelet medications, angiotensin-converting enzyme inhibitors, beta-blockers, and lifestyle changes, such as smoking cessation, weight reduction, regular exercise, stress reduction, and so on.

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Several randomized trials have compared percutaneous versus surgical revascularization for symptom relief and need for repeat revascularization as well as for reduction of death and myocardial infarction rates (1). Besides comparing revascularization strategies, these trials have shed light on the mechanisms of success and failure of each therapy. In this issue of the *Journal*, Alderman et al. (2) report data from a five-year angiographic follow-up of a subgroup of patients in the Bypass Angioplasty Revascularization Investigation (BARI) trial and implicate native disease progression as the leading mechanism of angina recurrence. This study, using detailed angiographic analysis, underscores the importance of disease-modifying treatments to complement revascularization procedures.

In the BARI trial, 1,829 patients with multivessel coronary artery disease were randomly assigned between 1988 and 1991 to balloon percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG). The five-year survival rate was similar for patients assigned to PTCA or CABG (86.3% vs. 89.3%, respectively; $p = 0.19$) (3). Systematic angiographic follow-up was performed in 5 of 18 centers and was completed in 79% of corresponding patients ($n = 407$). From this substudy, the authors report that the "culprit" for recurrence of angina five years after revascularization is predominantly the progression of native CAD and not necessarily the failure of the original revascularization procedure. There are several other noteworthy details in this important angiographic analysis.

The investigators in the BARI study used an angiographic score, a so-called myocardial jeopardy index (MJI), to measure the extent of CAD. The MJI was calculated from an anatomic representation of the size and distribution of those coronary arteries with ≥50% diameter stenosis. The BARI jeopardy score is notably different from other similarly intended scores, such as the Duke Jeopardy Score and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Lesion Score (4). Unlike these other scores, the BARI MJI uses a cut point of ≥50% diameter stenosis (rather than ≥70%), and it takes into account the size and length of the artery. This definition makes the MJI index potentially more representative of diffuse, moderate atherosclerotic disease. It may make this index less objective, although in the current study the authors reported high reproducibility. The one-year angiographic analysis from this same study group reported an odds ratio of 1.28 per 10% increase in MJI to predict angina, which is similar to that (1.22) reported in the present study (5). Although MJI has been shown to correlate with angina, there are several limitations of this methodology. This index does not take into account the presence of collateral circulation or myocardial scar (50% of the study population had a previous myocardial infarction). Even more relevant to the present study, this index does not take into account the type of vessel with stenosis. A 50% stenosis in a native vessel likely has different prognostic implication as compared with a 50% stenosis in a saphenous vein graft or a 50% restenotic lesion. Some studies have found the MJI of the BARI study to predict future adverse cardiac events (4), but the significance of this index is less certain for patients with previous or subsequent CABG.

In the current study, Alderman et al. (2) report MJI five years after randomization irrespective of intercurrent revascularization procedures. Repeat revascularization was performed in 53% of patients who were initially treated with balloon PTCA and 8% of the patients who were initially treated with CABG. As long as the repeat revascularization procedure was successful, the supplied area of myocardium at five years was considered to be "not jeopardized." In other words, this analysis included primary and secondary revascularization procedures at five years. It is well established that if restenosis does occur after balloon PTCA, it does so within the first year after the procedure, not later. Similarly, CABG compromise (beyond immediate graft failure) is roughly 10% in the first five years. With these caveats in mind, it is not particularly surprising that the leading cause for jeopardized myocardium during this study interval was

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the progression of native disease and not intermediate-term revascularization failure (35% vs. 21%).

This substudy highlights another interesting finding that can be interpreted in different ways. The authors note that at the time the BARI study was conducted, the "residual MJI" after balloon PTCA was higher than that after CABG (17% vs. 7%). On the other hand, the index PTCA was successful without recurrence of stenosis at five years in 61% of lesions, and 23% of recurrent lesions were successfully retreated. This resulted in only an 8% increase in the MJI in the PTCA group during the five years. Conversely, at late follow-up in the CABG group, 16% of vein grafts had ≥50% stenosis, and an additional 13% were totally occluded. This, combined with the compromise of 16% of left internal mammary artery grafts, resulted in a 13% increase in the MJI in the CABG group during the same time period. Therefore, although the MJI at five years was higher in the PTCA group compared with CABG group (25% vs. 20%), an impressive catch-up was observed for the CABG group.

Many factors could have contributed to this catch-up or surgical late-loss phenomenon. That revascularization failure was comparable between PTCA- and CABG-assigned patients (20% vs. 22%) at five-year follow-up is concerning for CABG because this usually marks the beginning of a higher attrition rate for vein graft conduits. Overall, disease progression in native vessels was more pronounced in patients treated with CABG. Disease progression was similar between the groups in untreated vessels (79% vs. 73%) but was more frequent in the CABG group for treated vessels (34% vs. 45%). It is possible that surgical manipulation somewhat contributed to lesion progression (e.g., probing the recipient vessel distal to graft anastomosis). Several studies have noted that lesions that are bypassed progress or narrow faster than the non-bypassed lesions (6), but the differences between revascularization strategies regarding native disease progression have not been well characterized. More importantly, whether this faster progression of atherosclerosis is clinically important is not known. The present study might suggest that the initial strategy of CABG results in worse progression of disease that leads to greater change in MJI as early as five years after the procedure.

In current practice, whether one form of revascularization is particularly better than the other is not possible to specifically answer from this analysis and, for that matter, from the original BARI study itself. The mechanics of PTCA and CABG have both changed significantly since the BARI study. Greater evolution has occurred in percutaneous revascularization, where a multiple-fold reduction in restenosis (from 1 in 3 to 1 in 20 patients) has taken place with drug-eluting stents (7). Furthermore, the procedural risk associated with percutaneous revascularization has substantially decreased (8). Coronary artery bypass graft surgery is now more frequently performed with one or more arterial conduits, but the impact of this change on reduction in long-term need for repeat revascularization is less certain.

It is sobering that the MJI experienced a catch-up phenomenon for the CABG cohort relative to the PTCA group. Previously, some authors have conjectured that placing a bypass graft not only treats the culprit lesion but the entire vessel proximal to the lesion and, therefore, provides better protection. These angiographic data do not confirm this hypothesis at five-year follow-up. Actually, it points to the possibility that lesion progression may be more frequent after CABG, and this may add to the risk of ischemia when the graft becomes compromised. Again, this is somewhat concerning because these data were taken at five years, a time when the saphenous vein graft failure rates have not yet peaked.

It must be recognized that in this entire discussion we have used "progression of atherosclerosis" very loosely. Angiography has been shown to be an inadequate tool to accurately assess disease progression. It is possible that negative remodeling of vessels contributes to smaller lumen and that the angiographic changes may not be solely from plaque progression (9). Furthermore, the current data are solely derived from an angiographic index, and no functional studies were performed to actually measure the volume of ischemic myocardium to incorporate the significance of scar, collaterals, or small-vessel disease. Unquestionably, the greatest implication of this study is to make patients and doctors more aware that the revascularization procedure is not a cure for atherosclerotic CAD.

Whichever method of revascularization is used, very aggressive risk factor modification should be pursued to prevent the progression of atherosclerosis. That the rate of tobacco use was unchanged from the index to follow-up angiography is distressing. The increasing use of statins is encouraging, but in these highly acclaimed medical centers, the rate of their use in this study was far from exemplary. It has been repeatedly shown that optimal treatment of patients with CAD results in better outcome (10). All efforts should be geared towards achieving this "simple" goal. Although these angiographic findings from the BARI study present more fodder to debate which revascularization strategy is better, we should not repeat the mistake of getting too close to the trees so as to lose sight of the forest. The major message from this analysis is that we should be very cognizant about the reality of CAD progression in a relatively short timeframe. We should not overemphasize the importance of the revascularization procedure choice but rather shift our focus from the vulnerable plaque to the vulnerable patient.

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