

*Editorials***MYOCARDIAL REVASCULARIZATION —  
BYPASS SURGERY OR ANGIOPLASTY?**

**I**N this issue of the *Journal*, the results of the Bypass Angioplasty Revascularization Investigation (BARI), a large clinical trial comparing coronary-artery bypass grafting (CABG) with percutaneous transluminal coronary angioplasty (PTCA), are presented.<sup>1</sup> BARI enrolled 1829 patients who were followed for an average of 5.4 years. The authors concluded that for patients with multivessel coronary artery disease and suitable anatomy who prefer to avoid major surgery, "angioplasty offers a reasonable alternative with an expectation of similar overall survival rates and survival rates free of Q-wave myocardial infarction."

This carefully worded conclusion is similar to that derived from a recent meta-analysis of eight smaller trials with a total of 3371 patients with single-vessel coronary disease (732 patients) or multivessel disease (2639 patients) followed for 1 to 4.7 years.<sup>2</sup> Readers may interpret these collective data to mean that PTCA and CABG have equivalent outcomes. The choice of procedure for individual patients may then be based on other factors, such as shorter hospital stays and avoidance of major surgery with PTCA, or lower rates of subsequent procedures and recurrent angina after CABG.<sup>1-6</sup> But is such a simple conclusion acceptable?

The aim of BARI was to determine whether an initial strategy of PTCA, as compared with CABG, compromises clinical outcome.<sup>7</sup> The primary end point was mortality at five years, which was found to be 13.7 percent for PTCA and 10.7 percent for CABG. The observed survival advantage at five years with CABG was 2.9 percentage points, with a 95 percent confidence interval of -0.2 to 6.0.<sup>1</sup> Thus, the study did not establish with certainty that an initial strategy of PTCA is actually equivalent to CABG in patients with multivessel disease and clinically severe angina or objective evidence of ischemia. In fact, the confidence interval is consistent with the possibility that the survival rate with CABG may be superior by as much as 6 percentage points. Stated differently, the data are consistent with a 50 percent higher mortality rate with PTCA.

Although not statistically significant, a somewhat higher mortality rate with PTCA was also reported in two other trials, the Emory Angioplasty Versus Surgery Trial (EAST)<sup>5</sup> and the Coronary Angioplasty versus Bypass Revascularization Investigation.<sup>8</sup> Combining all available data,<sup>1,2</sup> my colleagues and I calculated the risk ratios for mortality to be 1.25 (95

percent confidence interval, 0.75 to 2.07) at hospital discharge (favoring PTCA), 0.86 (95 percent confidence interval, 0.63 to 1.16) at one year, and 0.89 (95 percent confidence interval, 0.74 to 1.08) overall (favoring CABG). These differences are not statistically significant, and the confidence intervals are wide, because the total number of patients in these studies was limited. Thus, although a survival advantage with CABG is suggested, there is insufficient statistical power to be certain.

The relevance of small differences in survival may be questioned. Yet differences of similar relative and absolute magnitude have been reported in larger trials claiming important treatment benefits for patients with moderately elevated cholesterol levels or myocardial infarction. If differences in mortality on the order of 1 percent (10 deaths per 1000 patients treated) are considered relevant, larger trials are required to exclude such differences and to demonstrate equivalence.<sup>9</sup> It is remarkable that such larger trials are commonly conducted for medical treatment regimens, whereas comparative trials of interventional procedures such as BARI do not have sufficient statistical power to demonstrate or exclude similar differences. Furthermore, the difference between treatment regimens, if any, may become apparent only after long-term follow-up.

In BARI, myocardial infarction during the initial hospitalization was more frequent after CABG than after PTCA. Nevertheless, the rates of survival free from Q-wave myocardial infarction (80.4 percent after CABG and 78.7 percent after PTCA) were similar at five years.<sup>1</sup> The investigators correctly point out that the rates of infarction were underestimated, because only Q-wave myocardial infarctions were reported. This explains why the rates are lower than those in other recent trials in which serum creatine kinase MB values were used to detect infarctions associated with PTCA.<sup>7</sup> The interpretation of a composite end point, such as survival without myocardial infarction, becomes difficult if the various components are not affected in the same way. How should we interpret the somewhat better survival in spite of somewhat more frequent myocardial infarctions with CABG in BARI? Clearly, in this situation, more weight should be given to the survival advantage, albeit small. It is better to survive with an infarct than not to survive at all.

In BARI, as in the other studies, CABG provided more extensive revascularization, with an average of 3.1 grafts per patient, than PTCA, for which angioplasty was attempted for an average of 2.4 lesions.<sup>10</sup> This difference, along with the problem of restenosis, resulted in higher rates of angina and repeated revascularization procedures after PTCA.<sup>1-6</sup>

A subgroup analysis in BARI revealed a major advantage of CABG over PTCA in patients with treated diabetes. In fact, the higher mortality after PTCA

**TABLE 1.** ESTABLISHED AND POSSIBLE DIFFERENCES BETWEEN CABG AND PTCA.

CABG		PTCA	
ADVANTAGES	DISADVANTAGES	ADVANTAGES	DISADVANTAGES
Established Differences			
Results in more complete revascularization	Involves major surgery (possible perioperative problems)	Major surgery avoided in 70 percent of patients	Results in less complete revascularization
Provides excellent relief of angina	Requires longer hospitalization and higher initial costs	Associated with shorter hospitalization and lower initial costs	Angina may recur
Associated with fewer subsequent procedures			Associated with more subsequent procedures
Possible Differences			
Possibly better long-term survival	Associated with more early infarctions	Associated with fewer periprocedural infarctions	Possibly poorer long-term survival

(as compared with CABG) was accounted for by the higher rate in this subgroup of patients, which made up 19 percent of the study population. This important observation would have major implications for therapy in clinical practice if confirmed by data from other trials. However, in EAST, the mortality rate among diabetics in the PTCA group was not higher than in the CABG group,<sup>5</sup> although this population was much smaller. Additional analyses from the other trials may help to clarify this issue.

Many factors influence the choice of procedure for revascularization in a given patient (Table 1). The decision by the physician and the patient will depend on the weight given to the various factors.

In studies of interventional procedures, technology may change during the long interval between the enrollment of patients and the reporting of results. Consequently, the results of a trial may apply to procedures that are not fully comparable to those used currently. Indeed, major advances have been made in interventional cardiology. The use of blockers of platelet glycoprotein IIb/IIIa receptors may halve the rate of periprocedural myocardial infarction and improve long-term outcome.<sup>7</sup> Furthermore, the use of coronary stents improves outcome, particularly since the introduction of better deployment techniques, better antithrombotic regimens, and heparin-coated stents.<sup>11</sup> Also, surgical techniques continue to improve with more frequent use of internal-thoracic-artery grafts and, more recently, minimally invasive surgical procedures.<sup>12</sup>

In the past, CABG and PTCA were distinct procedures performed by separate groups of operators. In the near future we may expect more of a team approach and the development of larger revascularization centers in which different procedures are performed by a closely coordinated team of operators with different backgrounds. Such developments necessitate repeated reassessment of the relative strengths and weaknesses of surgical and percutane-

ous revascularization procedures. Studies of adequate size remain warranted in spite of the findings in BARI and other comparisons of coronary surgery and angioplasty.<sup>1-6</sup> In the meantime, the conclusions of the BARI investigators stand: in patients with myocardial ischemia and multivessel disease, who constitute 12 percent of all candidates for revascularization, surgery is the established therapy, and angioplasty is an acceptable alternative.

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## REFERENCES

1. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217-25.
2. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-9.
3. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *Lancet* 1995;346:1179-84.
4. RITA Trial Participants. Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. *Lancet* 1993;341:573-80.
5. Weintraub WS, Mauldin PD, Becker E, Kosinski AS, King SB III. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease: results from the Emory Angioplasty Versus Surgery Trial (EAST). *Circulation* 1995;92:2831-40.
6. Hamm CW, Reimers J, Ischinger T, Rupprecht H-J, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. *N Engl J Med* 1994;331:1037-43.
7. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.
8. Bertrand M. Overview of the European trials of PTCA and bypass surgery. Presented at the American Heart Association Meeting, November 13-15, 1995, Anaheim, Calif.
9. International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995;346:329-36.
10. Williams DO, Baim DS, Bates E, et al. Coronary anatomic and procedural characteristics of patients randomized to coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Cardiol* 1995;75:27C-33C.

11. Serruys PW, Emanuelsson H, van der Giessen W, et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries: early outcome of the Benestent-II Pilot Study. *Circulation* 1996;93:412-22.

12. Borst C, Jansen EWL, Tulleken CAF, et al. Coronary artery bypass grafting without cardiopulmonary bypass and without interruption of native coronary flow using a novel anastomosis site restraining device ("Octopus"). *J Am Coll Cardiol* 1996;27:1356-64.

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## PREGNANCY AND RENAL DISEASE

OF all the medical disorders that add risk to pregnancy, renal disease has long ranked among those most feared by physicians. Not only are the renal and vascular manifestations of preeclampsia the most common medical complication of pregnancy, affecting 5 to 7 percent of previously healthy women, but also intrapartum worsening of renal function, along with increased fetal morbidity and mortality, has been the fate of a large proportion of pregnant women with underlying diseases of the kidney, at least in the past.<sup>1</sup> Careful longitudinal studies of large numbers of women with varying degrees of renal impairment are necessary to permit us to advise concerned patients intelligently about the risks of pregnancy. The results of the study by Jones and Hayslett of 82 pregnancies in 67 women with moderate or severe renal insufficiency, reported in this issue of the *Journal*,<sup>2</sup> will help obstetricians and internists do just that. Such data are not easy to collect, because fertility is decreased in women with renal impairment.

For doctors who need to counsel women with renal impairment who are contemplating pregnancy, certain caveats must be kept in mind in interpreting these results. First, some women who do well may be lost to follow-up after pregnancy because they do not seek medical advice. On the other hand, longitudinal surveys of the outcome of pregnancy cannot include women who contemplated pregnancy but did not in fact become pregnant, perhaps on their doctors' advice. Such women may have a poorer prognosis than those who actually become pregnant.

The good news in this report is that with advances in the care of newborn babies, fetal survival has improved remarkably. This is important because almost 60 percent of infants born to women with a serum creatinine concentration exceeding 1.4 mg per deciliter (124  $\mu\text{mol}$  per liter) are premature — six times the expected rate in the general population — and because the babies are also small for their gestational age. Both problems are more marked, the worse the mother's renal insufficiency. Nevertheless, fetal mortality in the present report was only 7 percent, as compared with rates ranging from 12 to 88 percent

in earlier, smaller series of similar women.<sup>3-6</sup> With the advent of modern intensive care for newborns, survival is routine even when babies are born as early as 26 to 27 weeks of gestation.

The news is not so good for the mother. What is clear from all the published data is that, as the woman's degree of renal insufficiency increases, the risk that renal function will worsen during pregnancy rises sharply, a tendency that is further exaggerated by the presence of hypertension. Katz et al. found that renal function declined during pregnancy in 16 percent of women with mild renal disease (those with initial serum creatinine concentrations of less than 1.4 mg per deciliter), most of whom were normotensive.<sup>7</sup> Of the women followed by Jones and Hayslett whose initial serum creatinine concentrations were 1.4 mg per deciliter or more, almost half had a pregnancy-related decline in creatinine clearance of at least 25 percent, and in three quarters of these women, the decline in renal function persisted or progressed further after delivery. Among women whose initial serum creatinine concentrations were between 1.4 and 1.9 mg per deciliter (124 and 168  $\mu\text{mol}$  per liter), the chance of a pregnancy-related exacerbation was roughly 40 percent, and the loss of renal function persisted after delivery in about half of those affected.

The risk of pregnancy-related renal damage was found to be particularly high in the subgroup of women whose initial serum creatinine concentrations were 2.0 mg per deciliter (177  $\mu\text{mol}$  per liter) or higher. Of 20 pregnancies in such women, serum creatinine concentrations rose in the third trimester in 13 (65 percent). Worsened renal function persisted or progressed after delivery in almost all these women, rapidly reaching end-stage renal failure in seven (35 percent). Thus, unlike pregnancy in women with only mild renal disease, pregnancy in women with moderate or severe renal disease tends to exacerbate renal injury in a way that is largely irreversible. This conclusion is supported not only by the data of Jones and Hayslett, but also by earlier studies involving smaller numbers of women.<sup>3-6</sup> Although some of the late decline in kidney function may be attributed to the natural progression of the underlying disease, it is notable that in the present study all the women with peripartum worsening for whom preconception data were available had decreases in the glomerular filtration rate during pregnancy that exceeded those predicted.

There are, of course, exceptions to the general rule. One of the study patients had an initial serum creatinine concentration of 3.7 mg per deciliter (327  $\mu\text{mol}$  per liter) and had no change in renal function either during pregnancy or six weeks after delivery. Many nephrologists and obstetricians can recount such anecdotes. An optimistic physician or a woman yearning to bear a child may prefer to view