Better Outcome for Women Compared With Men Undergoing Coronary Revascularization

A Report From the Bypass Angioplasty Revascularization Investigation (BARI)

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Background—Numerous studies have shown that women undergoing coronary revascularization procedures do so at a higher risk for an adverse outcome compared with men. However, the impact of advances in technology and improvements in techniques on in-hospital and long-term outcome after revascularization in women is unclear.

Methods and Results—We evaluated 1829 patients with symptomatic multivessel coronary disease randomized to CABG or PTCA in the Bypass Angioplasty Revascularization Investigation (BARI), of whom 27% were women. As expected, women were older (64.0 versus 60.5 years), with more congestive heart failure (14% versus 7%), hypertension (68% versus 42%), treated diabetes mellitus (31% versus 15%), and unstable angina (67% versus 61%) than men but had similar preservation of left ventricular function and extent of multivessel disease. Women assigned to surgery received the same number of total grafts but fewer internal mammary artery grafts (72% versus 85%, \( P < 0.01 \)), and those assigned to angioplasty had more intended lesions (76% versus 71%, \( P < 0.01 \)) successfully dilated than men. At an average of 5.4 years’ follow-up, crude mortality rates were similar in women (12.8%) and men (12.0%). The Cox regression model adjusting for baseline differences revealed that women had a significantly lower risk of death (relative risk, 0.60; 95% CI, 0.43 to 0.84; \( P = 0.003 \)) but not a significantly lower risk of death plus myocardial infarction (relative risk, 0.84; 95% CI, 0.66 to 1.07; \( P = 0.16 \)) than men.

Conclusions—Although the unadjusted mortality rate suggests that women and men undergoing CABG and PTCA have a similar 5-year mortality, women have higher risk profiles; consequently, contrary to previous reports, female sex is an independent predictor of improved 5-year survival after we control for multiple risk factors. (Circulation. 1998;98:1279-1285.)

Key Words: coronary disease ■ angioplasty ■ surgery ■ women

Numerous studies evaluating the outcome of coronary revascularization performed with CABG or PTCA have reported higher rates of mortality and major complications in women compared with men.1–7 The factors responsible for this sex difference in outcome are uncertain, but advanced age, comorbid disease, hypertensive heart disease, and small vessel size in women may play a role.

Many of the earlier studies reporting sex differences in outcomes of CABG and PTCA were performed before major advances in technology and improvements in revascularization technique. It is possible that enhanced myocardial protection and use of arterial conduits during CABG and an increase in the availability and use of smaller guiding catheters and low-profile balloon catheters during PTCA may result in a more favorable outcome, particularly in women. In addition, few studies have compared long-term outcome in women and men after coronary revascularization.

Accordingly, to determine whether women have an unfavorable long-term outcome after CABG and PTCA compared with men, we evaluated patients undergoing revascularization within the Bypass Angioplasty Revascularization Investigation (BARI). The aim of the multicenter, NHLBI-funded BARI trial was to test the hypothesis that PTCA does not compromise long-term outcome compared with CABG in the treatment of patients with multivessel disease. Patients had to have severe myocardial ischemia and coronary anatomy...
amenable to both procedures. The primary end point of the study, total mortality at an average of 5.4 years of follow-up, was similar for both procedures, although mortality was significantly higher in a subgroup of treated diabetic patients assigned to PTCA.8

Methods

Study Protocol

The study design and protocol, patient selection, clinical and angiographic inclusion and exclusion criteria, procedural guidelines, definitions, and administrative structure have been published previously.9–12 In brief, patients with severe angina or myocardial ischemia and multivessel coronary disease amenable to both CABG and PTCA were randomly assigned to 1 procedure as an initial treatment strategy. Between August 1988 and August 1991, 1829 patients at 18 centers, 16 in the United States and 2 in Canada, were enrolled in the trial. The protocol was approved by the Institutional Review Board at participating institutions, and all patients provided written informed consent. Baseline clinical and angiographic characteristics, procedural factors, in-hospital mortality, myocardial infarction, major complications, and follow-up status, including death, myocardial infarction, symptoms of angina, and occurrence of repeated revascularization procedures, were compared between women and men. At the time of analysis, patients had been followed for an average of 5.4 years. Cause of death was classified by an independent mortality and morbidity classification committee.

Definitions

A Q-wave myocardial infarction was defined as a new 2-grade worsening in the Q wave according to the Minnesota Code10 or new left bundle-branch block pattern on ECG with abnormal cardiac enzyme levels (total creatine kinase twice the normal level and an abnormal MB isoenzyme level). A Q-wave myocardial infarction during the 96-hour period following a revascularization procedure was diagnosed solely on the basis of the Minnesota Code. Non-Q-wave myocardial infarction was diagnosed when the cardiac enzymes were elevated with angina for >20 minutes or with the appearance of new ECG changes. Diabetes was defined in terms of treatment with oral hypoglycemic agents or insulin. Hypercholesterolemia was defined as a history of total cholesterol >4.8 mmol/L. Hypertension was defined as a history of high blood pressure requiring drug treatment. Congestive heart failure was documented by a physician’s statement in the medical record supported by history and physical examination. Comorbidity was defined as the presence of chronic obstructive pulmonary disease, chronic renal failure, history of malignancy, or peripheral vascular disease. A significant coronary lesion was defined as a stenosis of ≥50% of the diameter of the vessel with a reference diameter of ≥1.5 mm as measured by electronic calipers. The extent of vessel disease was determined on the basis of the number of myocardial territories affected by significant lesions. The complexity of the lesions was categorized as type A, B, or C, according to the criteria of the American College of Cardiology/American Heart Association Consensus Panel.13 To estimate the amount of myocardium jeopardized by coronary arterial stenoses, the global percent jeopardy was calculated as the ratio of left ventricular territory attended by terminal coronary artery segments compromised by lesions with diameter stenoses >50% to the sum of all left ventricular territories supplied by major terminal coronary branches.12 Angiographic success after PTCA was defined as a reduction in the coronary stenosis of ≥20% to a residual stenosis of <50% in the presence of grade 3 TIMI flow.

Statistical Analysis

Sex differences in clinical and angiographic characteristics at baseline, procedural factors, and in-hospital complications were evaluated with the χ² test (or Fisher’s exact test) for categorial data and Student’s t test or Wilcoxon’s test for continuous data. CABG and PTCA were compared according to the principle of intention to treat.

Baseline Characteristics

The baseline clinical characteristics of the women and men are listed in Table 1. As expected, women were older than men (mean age, 64 versus 61 years), and a higher percentage of women were older than 65 years (49% versus 35%). Although there was no difference in the prevalence of prior myocardial infarction, there was a higher prevalence of congestive heart failure in women than men (14% versus 7%). There was also a higher prevalence of diabetes mellitus, history of hypercholesterolemia, and history of hypertension in women than in men, although there was a similar prevalence of current cigarette smokers. Unstable angina occurred more often in women (67% versus 61%). Comorbidity was present in more women than men (29% versus 23%).
The baseline angiographic characteristics of the patients are listed in Table 2. There was a similar occurrence of triple-vessel coronary disease and similar numbers of significant lesions, significant proximal lesions, significant proximal left anterior descending artery lesions, and total occlusions in women and men. Lesion morphology was also similar between groups. Although mean left ventricular ejection fraction was slightly higher in women, the proportion of left ventricular ejection fraction <0.50 was similar to that in men.

Procedural Factors
In patients assigned to CABG, there was no sex difference in the total duration of the surgical procedure, although cross-clamp time, expressed as the mean percent of the total bypass time, was significantly shorter in women than in men (56% versus 59%). The mean number of significant lesions and the number of total grafts were the same in women and men. However, internal mammary artery conduits were used in fewer women than men (72% versus 85%). Of note, all vessels intended for bypass were grafted in 89% of women compared with 92% of men (P=0.069).

In patients assigned to PTCA, the mean number of significant lesions (3.2) and the mean number of lesions intended for dilatation (2.6) were the same in women and men. Interestingly, multilesion angioplasty was attempted in more women (80%) than men (76%, P=0.03), and there also was a trend toward more multivessel angioplasty in women. Although angiographic success in attempted lesions was similar between women and men (80% versus 78%), angiographic success in intended lesions was higher in women (75% versus 71%) than in men. As expected, mean reference vessel diameter was smaller in women than in men (2.8 versus 2.9 mm, P=0.02).

In-Hospital Outcome
In patients undergoing an initial strategy of CABG, there was a similar incidence of death (1.3% versus 1.4%) and Q-wave myocardial infarction (4.7% versus 4.6%) in women and men, respectively. Of note, there was a higher incidence of congestive heart failure or pulmonary edema in women (9.8% versus 1.8%, P<0.001). In patients undergoing an initial strategy of PTCA, there was a similar low incidence of death (0.8% versus 1.2%) and Q-wave myocardial infarction (1.2% versus 2.4%) in women and men, respectively. There was also a similar incidence of emergency CABG and abrupt vessel closure. Again, in women undergoing PTCA, there was a higher incidence of congestive heart failure or pulmonary edema (4.8% versus 1.4%) than in men (P=0.005).

Comparison of treatment strategies within women shows a similar incidence of in-hospital death (1.3% versus 0.8%) but a higher incidence of Q-wave myocardial infarction (4.7% versus 1.2%, P=0.029) and congestive heart failure or pulmonary edema (9.8% versus 4.8%, P=0.052) in women undergoing CABG compared with PTCA.

Follow-Up Status
Anginal Status
As expected, at baseline, >90% of both women and men undergoing both CABG and PTCA were symptomatic. At 6 months, there was no difference in the incidence of angina between women and men in both treatment groups, although patients undergoing an initial strategy of PTCA were more likely to be symptomatic. In general, women experienced more angina than men. At 4 years, in patients undergoing an initial strategy of CABG, 18.8% of women compared with 13.2% of men (P=0.047) reported angina, whereas in patients undergoing an initial strategy of PTCA, 23.3% of women compared with 19.7% of men (P=0.27) reported anginal symptoms. At 5 years, symptomatic status was not significantly different between women and men.

Repeated Revascularization Procedures
The observations concerning repeated revascularization are depicted in Figure 1. In patients undergoing an initial strategy of CABG, women were significantly more likely to undergo a subsequent procedure, with a relative risk of 1.74 (P=0.043). In contrast, in patients undergoing an initial strategy of PTCA, women were significantly less likely than men to undergo a subsequent revascularization, with a relative risk of 0.74 (P=0.011).

### Table 2: Baseline Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Women (n=489)</th>
<th>Men (n=1337)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple-vessel disease, %</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Mean no. of significant lesions</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Mean no. of significant proximal lesions</td>
<td>0.99</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean no. of significant proximal LAD lesions</td>
<td>0.39</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean no. of significant diffuse lesions</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean no. of significant proximal LAD lesions</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean no. of significant class A lesions</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean no. of significant class B lesions</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean no. of significant class C lesions</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>58.8</td>
<td>56.9</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Myocardial jeopardy index</td>
<td>62.7</td>
<td>61.0</td>
</tr>
</tbody>
</table>

*P<0.01, women vs men.

LAD indicates left anterior descending artery.

Jacobs et al September 29, 1998 1281
Not surprisingly, women were less likely than men to undergo repeated revascularization with an initial strategy of CABG compared with PTCA (11.2% versus 51.9%, respectively; \( P<0.001 \)).

**Mortality and Myocardial Infarction**

Unadjusted 5-year survival for both treatment strategies is shown in Figure 2. The survival curves for women and men are virtually superimposable, so that at 5 years after revascularization, 87% of women and 88% of men were alive. Survival without myocardial infarction was achieved in 75% of women and 77% of men. Five-year survival without myocardial infarction was similar in women and men within both the CABG and PTCA groups.

Of note, 5-year survival (89% versus 86%, \( P=0.81 \); Figure 3) and survival free of myocardial infarction (76% versus 74%, \( P=0.28 \)) were similar in women treated with CABG and PTCA, respectively. The treatment difference among diabetic women (5-year survival, 72% for PTCA patients versus 83% for CABG patients; \( P=0.46 \)) was not statistically significant. Similar to the overall BARI trial, there was a significant treatment difference among diabetic men (5-year survival, 60% PTCA versus 79% CABG; \( P<0.001 \)).

In a multivariate Cox regression model, congestive heart failure and treated diabetes, as defined in BARI were strong predictors of 5-year mortality. In addition, older age and the presence of peripheral vascular disease imparted a higher risk of mortality. As expected, the presence of normal left ventricular function was a predictor of better survival. It is remarkable that female sex was also a predictor of higher survival, with women having 60% of the risk of mortality compared with men (95% CI, 0.43 to 0.84; \( P=0.003 \)) regardless of treatment assignment. With a multivariate Cox model, women also had a lower risk of death plus myocardial infarction (relative risk, 0.84; 95% CI, 0.66 to 1.07; \( P=0.16 \)) than men, but this was not statistically significant.

Because the randomized BARI population represents a selected group of patients undergoing coronary revascularization, data from the randomized cohort were pooled with data from the registry cohort (patients eligible but not randomized who consented to follow-up; \( n=2013 \)), and multivariate regression models for the combined group of patients who received a revascularization procedure within the first 3 months of enrollment were constructed. Of note, female sex was an independent predictor of improved survival (\( P<0.05 \)) in all models. The model that included those predictors related to mortality (\( P<0.15 \)) within the combined population revealed that female sex imparted a relative risk of 0.70 (95% CI, 0.54 to 0.91; \( P=0.007 \)).

**Discussion**

**Baseline Clinical and Angiographic Characteristics**

Although the incidence of coronary heart disease increases with age in women at a rate similar to that in men,\(^{90}\) the clinical presentation of the disease in women lags 10 to 20 years behind men. Therefore, it is not surprising that when women present for coronary revascularization, they are significantly older than men. Women also have a higher incidence of risk factors such as diabetes mellitus, hypercholesterolemia, and hypertension and more comorbid disease than men. These sex differences in patients with coronary artery disease have been remarkably consistent, as reported here and in numerous previous studies of coronary revascularization with both CABG and PTCA.\(^{1-7}\)

Despite the higher risk profile in women undergoing coronary revascularization, the extent of coronary disease is similar to that in men. Specifically, the prevalence of single-vessel and multivessel disease is notably not different between women and men. Although by design virtually all patients in BARI had multivessel coronary disease, the incidence of double- and triple-vessel disease and the total disease burden (number of total, proximal, and diffuse lesions and lesion morphology) were similar in women and men. Whether this finding suggests that the traditional risk factors for coronary heart disease are less potent in women or are influenced by estrogen levels is unclear, and the BARI trial did not collect data on hormone replacement therapy.

It is noteworthy that similar to previous studies, women in BARI had a higher incidence of unstable angina and a higher functional class of stable angina than men. The overall higher level of symptoms in women is intriguing. Whether the increased incidence of unstable angina in women represents a sex difference in the pathophysiology of the ruptured plaque\(^{20}\) or a higher degree of endothelial dysfunction in the setting of increased hypertension and hypercholesterolemia remains speculative.

Although women undergoing coronary revascularization usually have a similar (or smaller) number of previous...
myocardial infarctions and better left ventricular function, the incidence of clinical congestive heart failure is significantly higher than for men. These observations are particularly important in BARI because the incidence of periprocedural congestive heart failure or pulmonary edema was significantly higher in both treatment strategies in women compared with men. Diastolic dysfunction on the basis of advanced age and hypertensive heart disease in women has been proposed as the basis for these findings. In patients undergoing CABG, congestive heart failure has been shown to account for the excess mortality in women, and congestive heart failure is an independent predictor of mortality in both women and men in BARI and in other trials. It has been postulated that the hypertrophied ventricle (notably more prevalent in women) may be less likely to tolerate volume shifts and transient ischemic periods associated with coronary revascularization.

Procedural Factors
Although the number of total grafts received was similar in women and men in the CABG group, significantly fewer internal mammary artery conduits were used, and there was a trend toward less complete revascularization in women undergoing CABG compared with men. These findings may account for the slightly shorter cross-clamp time noted in women. The less frequent use of internal mammary artery conduits in women, similar to other studies, is curious and appears to be unrelated to the incidence of left anterior descending artery disease, diabetes, or unstable symptoms. In fact, female sex and advanced age (>70 versus <60 years) were independent predictors of a decreased use of internal mammary artery conduits in BARI.

The observations regarding sex differences in multileesion and multivessel PTCA are of interest. The plan or practice of staging the procedure in patients with multivessel disease is based on many factors, including length of the procedure, amount of contrast used, and angiographic results achieved after dilatation of the first lesion. The observation that women underwent more multileesion PTCA and a trend toward more multivessel PTCA are unexplained but may be due in part to a higher incidence of staged procedures in women. Although angiographic success of attempted lesions was similar in women and men, angiographic success of intended lesions was higher in women because complete revascularization (number of intended lesions successfully dilated) was achieved more often in women.

In-Hospital Outcome
It is particularly noteworthy that in-hospital mortality was similar in women and men in both the CABG and PTCA groups. This finding is in contrast to previous reports, particularly in patients undergoing CABG; numerous studies have reported an ∼2.5-fold-higher mortality in women. Sex differences in mortality have been less consistent in patients undergoing PTCA, with mortality lower for women more recently but still higher compared with men. In the multicenter 1985 to 1986 NHLBI PTCA Registry, in-hospital mortality was ∼10-fold higher (2.6% versus 0.3%) in women compared with men, and female sex was an independent predictor of death. However, similar to the results reported here, the incidence of myocardial infarction and emergency CABG was similar in women and men. The reasons for the apparent relative improvement in mortality in women are unclear, but patient selection and improvements in technology and procedural techniques may be contributing factors.

Long-Term Outcome
Women had more angina than men during follow-up, and at certain times, this difference reached statistical significance. Perhaps this is accounted for by the use of fewer internal mammary artery conduits and less complete revascularization in women than men in the CABG group, as noted previously, and is related to a higher likelihood of a woman undergoing subsequent revascularization procedures after an initial strategy of CABG. The relative risk of undergoing subsequent revascularization after initial PTCA was lower in women. Perhaps this is due to more complete revascularization with PTCA compared with men. However, this remains speculative because more complete revascularization could be expected to result in a higher incidence of restenosis.

It is remarkable that at an average of 5.4 years after revascularization, mortality and mortality plus myocardial infarction were the same for women and men in both treatment strategies. In addition, women fared equally well with an initial strategy of CABG or PTCA. For total mortality, the magnitude of the treatment difference among diabetic women was smaller compared with diabetic men. However, the lack of statistical significance between treatment strategies in diabetic women is partially due to the relatively small sample size compared with men. In fact, the interaction between treatment and sex in terms of 5-year survival was not significantly different (P=0.12) in BARI diabetic patients. These results are consistent with the overall BARI trial, revealing a survival advantage in diabetic patients undergoing an initial strategy of CABG compared with PTCA.

Similar to the results reported here, a few large-scale studies have noted a similar mortality in women and men 10 years after hospital discharge (despite a higher in-hospital mortality) after undergoing CABG. However, reports of sex differences in long-term outcome after PTCA are limited. In the 1985 to 1986 NHLBI PTCA Registry, at 4 years of follow-up, women had a significantly lower event-free survival than men, but this was accounted for by baseline differences such as advanced age and comorbid disease in women. Despite these same baseline clinical and angiographic (ie, smaller vessel size in women) sex differences in patients undergoing revascularization in BARI, in-hospital and 5-year outcome in women and men did not differ. The reasons for this relative improvement in outcome in women are uncertain, but several factors should be considered. Although the baseline clinical and angiographic differences in women and men and the percent of women undergoing revascularization in BARI are consistent with previous reports, BARI patients represent selected patients with multivessel disease deemed to be amenable to both revascularization strategies performed in multiple centers by experienced operators. BARI was undertaken at a time when improvements in technology (excluding percutaneous coro-
nary devices) had occurred that perhaps imparted a relatively more favorable outcome in women. In addition, the potential for greater improvement in risk factor modification in women, despite a higher risk factor profile at baseline, needs further clarification.

What is clear, however, is that in the BARI population, mortality and mortality plus myocardial infarction both in-hospital and 5 years after coronary revascularization are similar in women and men undergoing both CABG and PTCA. Therefore, after adjustment for a higher baseline risk status in women, female sex is an independent predictor of better 5-year survival after revascularization in BARI.

With the focus on women’s health issues and specifically heart disease in women, it is important not to overemphasize sex differences but rather to concentrate on the outcome in women. The results of the BARI trial suggest that both CABG and PTCA are equally safe and effective procedures in women and therefore that these treatment strategies should be offered to women in need of revascularization with anticipation of excellent acute and long-term results.

Study Limitations

Certainly, interpretation of these results must take into account that the data come from a randomized clinical trial. Similar to most clinical trials with detailed inclusion and exclusion criteria, the BARI population is not representative of all patients undergoing coronary revascularization. Therefore, we examined BARI screening data to determine whether women were disproportionately excluded from the trial population. If there were an exclusion discrepancy by sex, we would expect that higher-risk women were not included in the trial while similar high-risk men were, thus explaining why BARI results may differ from other populations. However, among patients eligible for the trial women and men were equally likely to consent to randomization. In the trial, 26.7% of patients were women, while among patients eligible but not randomized, 25.8% were women.

Other important data from an ancillary BARI study conducted at a sample of all hospitals in the United States performing CABG and PTCA during the same time period as the BARI trial indicated that the proportion of women among all revascularization procedures at BARI sites was 27% and among all revascularization procedures at a random sample of hospitals around the country was 26%. Because these figures are similar to the 26.7% of women in the trial, there does not appear to be a sex bias for selection into the BARI trial. In addition, when the randomized and registry patients were combined, female sex was still an independent predictor of improved survival at 5 years.

In addition, patients in a randomized clinical trial may be an ideal group for studying sex differences because the rigorous trial design ensures that the women and men are reasonably comparable. In fact, all patients were treated by the same group of cardiologyists and surgeons and all met the same inclusion and exclusion criteria. The relative homogeneity of the population allows comparisons to be made about sex without nearly as much as concern about confounding as in an entire population of patients. Therefore, the independent effect of sex can be evaluated.

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References


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