JACC Vol. 25, No. 5
April 1995:1000–9

Comparison of 15-Year Survival for Men and Women After Initial Medical or Surgical Treatment for Coronary Artery Disease: A CASS Registry Study

KATHRYN B. DAVIS, PHD, FACC, BERNARD CHAITMAN, MD, FACC,*
THOMAS RYAN, MD, FACC,† VERA BITTNER, MD, FACC,‡ J. WARD KENNEDY, MD, FACC
Seattle, Washington; Saint Louis, Missouri; Boston, Massachusetts; and Birmingham, Alabama

Objectives. **This study compared the rates of coronary artery bypass graft surgery and 15-year survival for men and women after initial medical or surgical management.**

Background. **There has been concern that women with coronary artery disease are managed differently than men and that men and women have a different prognosis. The Coronary Artery Surgery Study (CASS) registry is a large data base of well characterized patients with long-term follow-up.**

Methods. **Patients underwent cardiac catheterization at 1 of 15 hospitals during 1974 to 1979. Bypass surgery rates were based on 12,452 men and 2,366 women. Survival results were based on 6,018 men and 1,095 women with operable coronary artery disease and initial medical management and 6,922 men and 1,291 women initially managed surgically.**

Results. **At 15 years, bypass surgery rates were 75% for men and 72% for women ($p = 0.91$). The rates remained similar after adjustment for clinical and angiographic variables. The 15-year survival rate was 50% for men and 49% for women with initial medical treatment ($p = 0.53$) and 52% for men and 48% for women ($p = 0.004$) with initial surgical treatment, a difference similar to that for operative mortality (men 2.5%, women 5.3%, $p < 0.0001$). Survival was improved by bypass surgery in most subgroups, with largest relative risks for high risk patients. Relative risks were similar for men and women.**

Conclusions. **The rate of bypass surgery did not differ between men and women. There were few differences in the survival of men and women. In general, both men and women with initial surgical treatment survived longer, although benefits were clinically and statistically significant only in those at high risk. The benefit was similar in both men and women.**

(J Am Coll Cardiol 1995;25:1000–9)

In January 1992, the National Heart, Lung, and Blood Institute convened an invitational conference entitled "Cardiovascular Health and Disease in Women" (1) to highlight new information derived from epidemiologic and clinical research. The conference recommended that information from existing clinical trials and registries be analyzed to compare the features of coronary heart disease in women and men with respect to baseline characteristics, clinical manifestations, responses to treatment and clinical outcomes (1). The present report presents the 15-year survival for men and women in the Coronary Artery Surgery Study (CASS) registry who had either initial medical or surgical management. The purpose of this report was to determine whether clinically comparable men and women are referred for bypass surgery at the same rate and whether they have similar survival with initial medical and surgical therapy.

In recent years there has been increasing concern about the management of women with ischemic heart disease. Some investigators (2,3) have suggested that men and women have been managed differently when presenting with symptoms or signs of myocardial ischemia and that women are less likely to have appropriate diagnostic evaluation and referral for coronary angiography. The appropriateness of referral for angiography cannot be addressed by CASS registry data because patients were entered into the registry after coronary arteriography. However, we were able to evaluate bypass surgery in patients who were evaluated for this procedure by angiography and to adjust the rates of surgical intervention in men and women for both clinical and angiographic patient characteristics. Evaluation of referral for bypass surgery and the subsequent 15-year survival period provides useful information with regard to physician management of men and women with established coronary artery disease between 1974 and 1979 and the resultant long-term outcome.

From the Department of Biostatistics and Division of Cardiology, University of Washington, Seattle, Washington; *Division of Cardiology, Saint Louis University Health Sciences Center, Saint Louis, Missouri; †Section of Cardiology, Boston University Medical Center, Boston, Massachusetts; and ‡Division of Cardiovascular Disease, University of Alabama School of Medicine, Birmingham, Alabama. This study was supported by a grant from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received March 27, 1994; revised manuscript received September 22, 1994, accepted November 9, 1994.

Address for correspondence: Dr. Kathryn B. Davis, 1107 NE 45th Street, Room 530, Seattle, Washington 98105.

0735-1097/95/$9.50
0735-1097(94)00518-U

Methods

Patients. The CASS trial was initiated in 1972 by the National Heart, Lung, and Blood Institute to compare coronary artery bypass graft surgery with conventional medical therapy for coronary artery disease. Complete details of the CASS design and protocol have been published elsewhere (4). The study was carried out at 15 participating medical centers in the United States and Canada and was designed as a randomized trial within a larger registry. For the registry, every patient who had coronary angiography for evaluation of suspected ischemic heart disease during the period of enrollment from 1974 to 1979 was asked to participate. Patients were enrolled after giving informed consent. The 24,958 registry patients comprised 94% of the patients eligible to enter the CASS registry. Annual follow-up of the registry was solicited through November 1982, with follow-up obtained in 99% of patients. A follow-up questionnaire was administered by mail between 1988 and 1991, with response obtained in 94%. Vital status was determined through 1989 by the National Death Index for most of the remaining patients.

There are 18,876 men and 6,082 women in the CASS registry population. Of these, 1,250 men and 241 women were excluded from the present analysis because they had had previous cardiac surgery. In the remaining 23,467 patients, 4,486 men and 3,401 women were excluded because they did not meet the definition of operable coronary artery disease. A patient was considered to have operable coronary disease if there was at least one major vessel with at least 50% stenosis and a distal vessel of normal size. In addition, there had to be at least 70% stenosis in a one of the coronary artery segments. Of the patients excluded for nonoperable coronary disease, 2,121 men (11%) and 2,343 women (39%) had normal coronary arteries. Nineteen patients with operable coronary disease had zero-vessel disease by CASS definition and were grouped with patients with single-vessel disease for the present analysis.

Statistical analysis. *Rates of bypass surgery* over time after angiography were estimated by Kaplan-Meier time-to-event analyses. Randomized patients were excluded from analyses of bypass surgery rates. Patients who died were censored at time of death. Comparison of rates between men and women was adjusted for differences between these two populations with regard to distribution of number of vessels diseased and Canadian Cardiovascular Society classification by using a stratified log-rank test. The comparison was adjusted for other covariates by using the Cox regression model for survival analysis, including terms for interaction with gender.

Survival rates for men and women were estimated to 15 years and compared by the log-rank statistic and Cox regression analysis. Survival experience to 8 years for medically and surgically treated patients was also compared by the log-rank statistic and Cox regression analysis. Beyond 8 years, survival experience for medically and surgically treated patients was compared by the difference in truncated mean survival estimates (5,6). Mean survival truncated at 14 years was chosen as the longest period over which mean survival could reliably be estimated for all subgroups of interest. This measure of survival is equal to the area under the survival curve truncated at 14 years. Mean survival was used because the survival curves for medically and surgically treated patients began to come together after 8 years, and proportional hazards could not be assumed.

Patients were considered to be medically treated if they did not have bypass surgery within the time period at each center during which 95% of the operations in the first year occurred; other patients were considered to be surgically treated. Survival for surgical patients was dated from the time of operation. Survival for medical patients was dated from the average time to operation at each center, which excluded 200 men and 54 women without bypass surgery because they died before the average time to operation. This method eliminates the bias that occurs when all the early deaths are included in the medical group.

Covariates included in the Cox analyses were gender, age, current smoker, former smoker, diabetes, hypertension, peripheral artery disease, angina, unstable angina, Canadian Cardiovascular Society angina class, number of major coronary arteries diseased (one to three), inferior myocardial jeopardy, anterior myocardial jeopardy, percent left main coronary artery stenosis, previous myocardial infarction, congestive heart failure score and left ventricular score. First, a model was built that included gender and all covariates, with backward elimination of the covariates until only the covariates with $p < 0.001$ remained. Interactions of gender with each of the covariates left in the model were then added to the model, and backward elimination of the interactions was done until only interaction terms with $p < 0.001$ remained. The p value for gender reported in each analysis is the value when only covariates with $p < 0.001$ were in the model. These covariates are listed for each analysis.

Results

Patient characteristics. Characteristics of the 12,940 men and 2,386 women who had operable coronary disease and were included in the medical–surgical comparisons are presented in Table 1. For the whole group the average age was 57 years for women and 54 for men ($p < 0.0001$). Women were more likely to have diabetes; men were more likely to be former smokers. Women had significantly more class III and IV angina and angina unrelated to exertion. Men had more three-vessel disease than women. The prevalence of left main coronary artery disease was similar. Table 2 shows the distribution of the severity of angina as related to number of diseased vessels. Given the same number of diseased coronary arteries, women had more class III to IV angina and angina unrelated to exertion (Fig. 1).

Paradoxically, women more often had a history of congestive heart failure, whereas men more often had a history of myocardial infarction and worse left ventricular scores.

Rates of coronary bypass surgery. There were 12,452 nonrandomized men and 2,366 nonrandomized women who had

JACC Vol. 25, No. 5
April 1995:1000–9

Table 1. Baseline Characteristics

	Initial Medical Therapy*		Initial Surgical Therapy*	
	Men (n = 6,018)	Women (n = 1,095)	Men (n = 6,922)	Women (n = 1,291)
Mean (±SD) age (yr)	52.9 ± 9.0	55.7 ± 9.4	54.6 ± 8.5	57.5 ± 8.7
CCS class				
No angina	26%	17%	8%	5%
I	7%	3%	4%	3%
II	31%	23%	22%	15%
III	22%	33%	38%	38%
IV	7%	13%	21%	31%
Angina unrelated to exertion	7%	11%	8%	9%
Unstable angina	20%	32%	41%	52%
Congestive heart failure	12%	21%	9%	14%
Hypertension	32%	49%	33%	50%
Diabetes	11%	18%	11%	16%
Peripheral arterial disease	10%	14%	10%	14%
Smoker				
Current	35%	36%	30%	35%
Former	49%	31%	52%	32%
Never	16%	33%	19%	33%
Previous MI	65%	55%	56%	48%
Extent of disease				
0–1 vessel	36%	49%	16%	24%
2 vessels	33%	29%	31%	34%
3 vessels	31%	22%	53%	43%
LMCA disease	4%	4%	14%	12%
Mean (±SD) left ventricular score	9.2 ± 4.3	8.4 ± 4.2	8.3 ± 3.7	7.6 ± 3.5

*$p < 0.0001$ for all differences between men and women within treatment groups, except p = NS for left main coronary artery (LMCA) disease. CCS = Canadian Cardiovascular Society; LV = left ventricular; MI = myocardial infarction.

operable disease. The rates of men and women undergoing coronary artery bypass surgery were similar (Fig. 2). One year after angiography, the rate was 57% for men and 58% for women. By 15 years, the bypass surgery rate was 75% for men and 72% for women (p = 0.91).

When patients were stratified by number of diseased coronary arteries, it appeared that more women than men had bypass surgery at 1 year: 38% of women versus 36% of men with one-vessel disease (p = 0.21); 62% of women versus 56% of men with two-vessel disease (p = 0.0003); and 74% of women versus 70% of men with three-vessel disease (p = 0.0006). When adjusted by stratification for the different distribution of number of diseased vessels in the male and female populations, the bypass surgery rates over 15 years were significantly higher for women (p = 0.0004). In contrast, when patients were stratified by angina class, it

Table 2. Angina Classification According to Extent of Coronary Artery Disease in Men and Women*

	No Angina	CCS Class I–II	CCS Class III–IV	Angina Unrelated to Exertion	Total No. of Pts
1-vessel disease					
Men	709 (22)	1,129 (35)	1,138 (35)	294 (9)	3,270
Women	140 (17)	213 (25)	405 (48)	88 (10)	846
2-vessel disease					
Men	732 (18)	1,358 (33)	1,739 (42)	320 (8)	4,149
Women	62 (8)	150 (20)	462 (62)	73 (10)	747
3-vessel disease					
Men	652 (12)	1,558 (28)	2,964 (54)	345 (6)	5,519
Women	51 (6)	144 (18)	527 (67)	70 (9)	792
Total					
Men	2,093 (16)	4,045 (31)	5,841 (45)	959 (7)	12,938
Women	253 (11)	507 (21)	1,394 (58)	231 (10)	2,385

*Two men and one woman with incomplete data were excluded. Data presented are number (%) of patients (Pts). CCS = Canadian Cardiovascular Society.

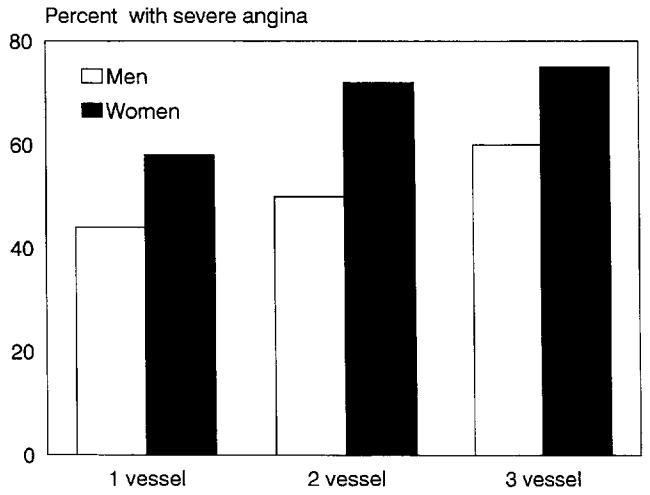

Figure 1. Percent of men and women with single-, double- and triple-vessel coronary artery disease and Canadian Cardiovascular Society class III or IV angina or angina unrelated to exertion.

appeared that relatively more men had bypass surgery ($p < 0.0001$).

When both number of diseased vessels and angina class were considered, there was no difference in the rates of bypass surgery for men and women ($p = 0.35$ by the stratified log-rank test). These covariates, along with age, current smoking, peripheral arterial disease, unstable angina, percent left main coronary artery stenosis, inferior myocardial jeopardy, anterior myocardial jeopardy and left ventricular score, were used in a Cox regression model with gender. The results of this analysis indicate that gender was not significantly related to selection of patients for bypass surgery ($p = 0.11$).

Survival with initial medical management. There were 6,018 men and 1,095 women with operable disease who did not have early coronary artery bypass surgery. The survival rate at 15 years was 50% for men and 49% for women ($p = 0.53$) (Fig. 3). During this period, 24% of these women and 28% of these men had bypass surgery.

The 15-year survival rate was similar for men and women within categories of angina: 54% in women and 50% in men without angina ($p = 0.12$); 58% in men and 57% in women with class I or II angina ($p = 0.67$); and 42% in both men and women with class III or IV angina or angina unrelated to exertion.

Survival was not significantly different ($p > 0.11$) between men and women with one- and two-vessel disease. However, the 15-year survival rate for men with three-vessel disease was much higher than that for women (34% versus 19%, respectively, ($p < 0.0001$).

In patients with a normal or minimally abnormal left ventricular score <10, the 15-year survival rate was 64% for men and 59% for women ($p = 0.07$). For those with a left ventricular score ≥10, the 15-year survival rate was 30% in men and 27% in women ($p = 0.16$). There was a marked interaction between left ventricular score and presence of three-vessel disease (Fig. 4). For patients with three-vessel disease and a left ventricular score <10, the 15-year survival rate was 52% for men and 28% for women ($p < 0.0001$). For those with three-vessel disease and a left ventricular score ≥10, the 15-year survival rate was poor for both men and women (18% vs. 12%, respectively, $p = 0.03$).

To determine the effect of gender on predicting survival with initial medical therapy, the patient's gender was entered into a Cox regression model along with age, current smoking, diabetes, hypertension, congestive heart failure score, previous myocardial infarction, left ventricular score, percent left main coronary artery stenosis and number of vessels diseased. When this was done, gender was not a significant predictor of survival (0.94 relative risk for women, $p = 0.29$). When interactions were added, there was a significant negative interaction of gender with left ventricular score (higher risk in men than women with severe left ventricular dysfunction, $p < 0.001$) if the interaction of gender with number of diseased vessels (higher risk in women than men with three-vessel disease, $p = 0.01$) was also in the model.

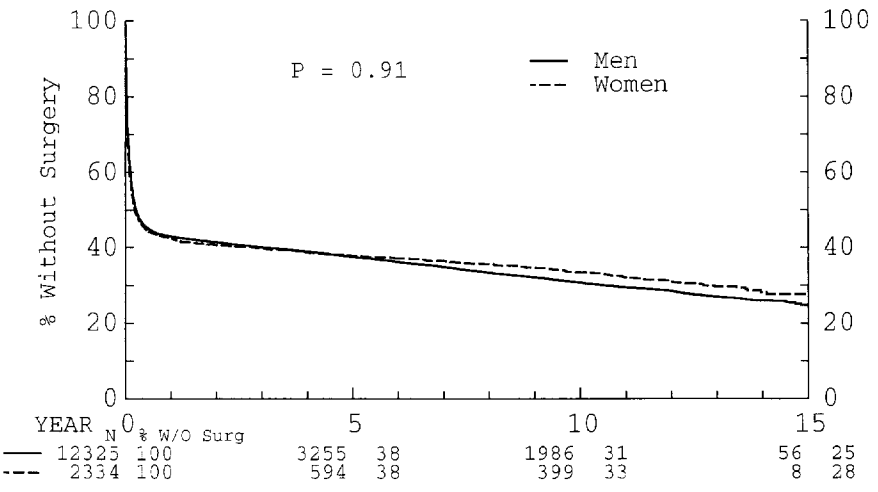

Figure 2. Percent of men and women with at least one vessel suitable for coronary bypass surgery who did not have bypass surgery over 15 years of follow-up.

JACC Vol. 25, No. 5
April 1995:1000–9

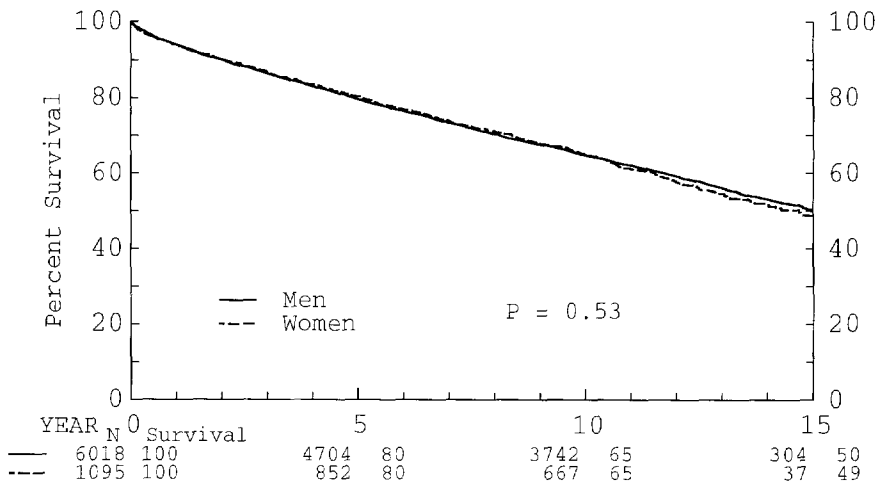

Figure 3. Percent survival of men and women with initial medical management.

Survival with initial surgical management. There were 6,922 men and 1,291 women with operable disease who had early coronary artery bypass surgery. Operative mortality rate was 2.5% in men and 5.3% in women ($p < 0.0001$). Survival rate at 15 years was 52% in men and 48% in women ($p = 0.004$), a difference similar to the initial difference in operative mortality rates (Fig. 5).

Differences in long-term survival were minor for men and women within categories of preoperative angina. At 15 years the survival rate was 52% in men and 53% in women without preoperative angina ($p = 0.49$) and 60% in both men and women with class I or II angina before bypass surgery. In patients with class III or IV angina or angina unrelated to exertion, the 15-year survival rate was 47% in men and 43% in women ($p = 0.03$).

The primary differences in 15-year survival between men

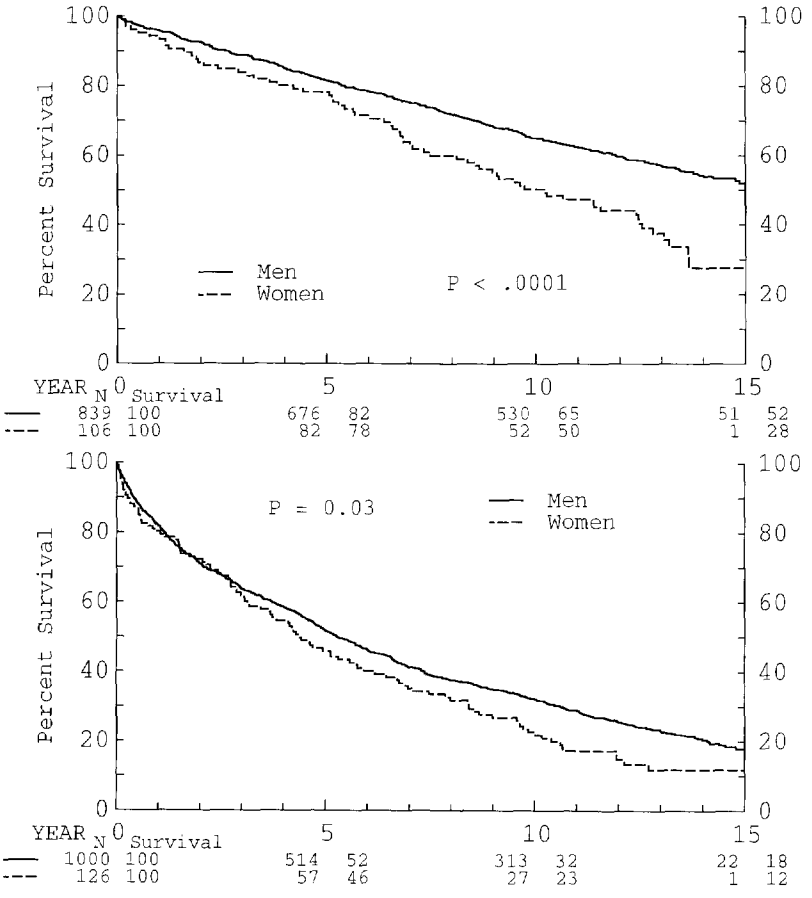

Figure 4. Percent survival of men and women with three-vessel disease and a left ventricular score <10 (**top**) or ≥10 (**bottom**) who underwent initial medical management.

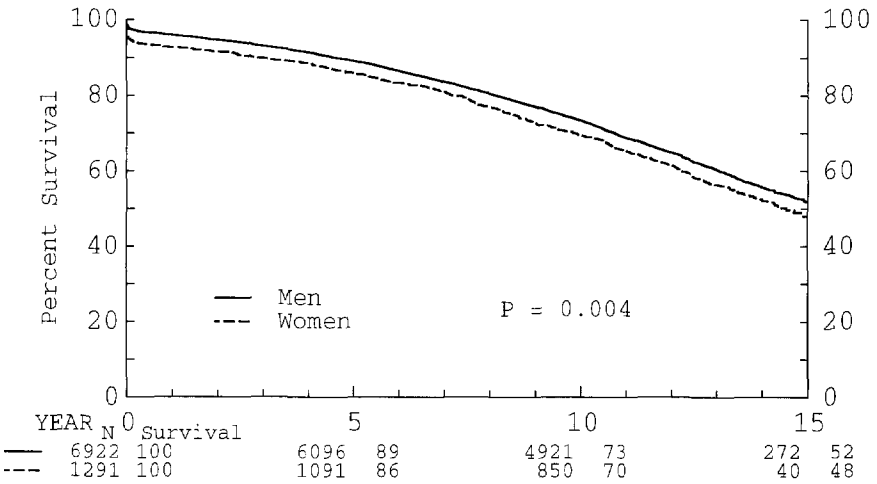

Figure 5. Percent survival of men and women with initial surgical management. Operative mortality was 2.5% in men and 5.3% in women.

and women occurred in patients with more severe coronary artery disease. For one-vessel disease, the 15-year survival rate was 66% in men and 69% in women ($p = 0.89$), and the operative mortality rate was 1.1% in men and 3.3% in women ($p = 0.006$). For two-vessel disease, the 15 year survival rate was 56% in men and 51% in women ($p = 0.04$), and the operative mortality rate was 1.9% in men and 5.1% in women ($p = 0.0001$). For three-vessel disease, the 15-year survival rate was 45% in men and 32% in women ($p < 0.0001$), and the operative mortality rate was 3.2% in men and 6.7% in women ($p < 0.0001$). This difference in 15-year survival for patients with three-vessel disease was significant ($p = 0.001$) even when operative mortality was excluded.

For patients with a left ventricular score <10, the 15-year survival rate was 60% in men and 52% in women ($p = 0.0009$), and the operative mortality rate was 1.6% in men and 4.7% in women ($p < 0.0001$). The survival rate at 15 years for patients with a left ventricular score ≥10 was 36% in men and 32% in women ($p = 0.002$), and the operative mortality rate was 4.2% in men and 7.8% in women ($p = 0.005$). The difference was greatest for patients with three-vessel disease and a left ventricular score ≥10. At 15 years, the survival rate was 32% for men and 21% for women ($p < 0.0001$), and the operative mortality rate was 4.7% for men and 8.4% for women ($p = 0.03$). For patients with three-vessel disease and a left ventricular score <10, the operative mortality rate was 2.3% for men and 6.4% for women ($p < 0.0001$), and the 15-year survival rate was 54% for men and 37% for women ($p = 0.0004$).

The differences in survival between men and women that were observed in some subcategories were a result of many factors that influence risk. Gender did not add significant predictive information (0.96 relative risk for women, $p = 0.43$) when it was included in a Cox regression model with age, current smoking, diabetes, hypertension, peripheral arterial disease, congestive heart failure score, left ventricular score and number of vessels diseased. There were no significant ($p < 0.001$) interactions with gender.

Comparison of survival with initial medical or surgical therapy. The 8-year survival data for categories of left ventricular score, age and number of vessels diseased are shown in Table 3 for men and women who had initial medical or surgical therapy. In almost every category the proportion surviving at 8 years is larger for patients with initial surgical management. In only three of these categories was initial medical therapy superior to initial surgical therapy (relative risks <1, and none of these is statistically significant). The relative risks are greatest for those patients at highest risk, including those with three-vessel disease or a left ventricular score >9 and those >64 years old. The difference in relative risks for men and women was tested by using gender, therapy, age, left ventricular score and number of vessels diseased in a Cox model of 8-year survival with an interaction term for each covariate with therapy. The individual terms and the terms for interaction with therapy were each significant ($p < 0.0001$) for the other covariates, but the interaction term for gender and therapy was not significant ($p = 0.57$). Thus, the benefit of bypass surgery is similar for men and women, as indicated in Table 3 by the similarity of the relative risks for men and women within each subcategory of the other covariates.

Overall survival to 15 years is shown for medically and surgically managed men and women in Figure 6. The mortality rate of patients managed with initial bypass surgery increased after 8 years, probably as a result of closure of the saphenous vein grafts, so that at 15 years the survival rates were similar for surgically and medically managed patients. Even though the survival rates at 15 years were similar, mean survival time was greater for patients initially treated with bypass surgery. Mean survival time, truncated at 14 years for several subgroups, is shown in Table 4. As was the case with 8-year survival rates, the benefit of initial bypass surgery in terms of extended years of life over 14 years of follow-up is greatest in those patients at highest risk. For patients <65 years old, with a left ventricular score <10 and one-vessel disease, the added years of life were only 0.1 year for men and women. For patients >64 years old

JACC Vol. 25, No. 5
April 1995:1000–9

Table 3. Eight-Year Percent Survival and Relative Risk for Men and Women With Initial Medical or Surgical Management

	Single-Vessel CAD			Double-Vessel CAD			Triple-Vessel CAD		
	Medical	Surgical	Rel Risk	Medical	Surgical	Rel Risk	Medical	Surgical	Rel Risk
LV score <10									
Age <65 yr									
Men	1,436 (89)	854 (92)	1.04*	1,063 (84)	1,367 (89)	1.06*	732 (75)	1,836 (83)	1.11*
Women	348 (89)	242 (92)	1.03	169 (80)	259 (82)	1.03	74 (62)	259 (77)	1.26*
Age ≥65 yr									
Men	91 (70)	54 (76)	1.08	84 (68)	141 (82)	1.20*	116 (53)	315 (72)	1.36*
Women	52 (87)	30 (80)	0.92	34 (65)	60 (73)	1.12	32 (56)	99 (73)	1.30
LV score ≥10									
Age <65 yr									
Men	553 (75)	149 (82)	1.09	726 (60)	527 (76)	1.27*	840 (41)	1,160 (69)	1.70*
Women	107 (70)	25 (67)	0.96	77 (54)	76 (72)	1.33*	88 (36)	112 (58)	1.62*
Age ≥65 yr									
Men	29 (48)	26 (69)	1.43	70 (36)	63 (59)	1.64*	160 (22)	193 (53)	2.47*
Women	20 (64)	4 (50)	0.79	21 (43)	24 (66)	1.54	38 (22)	54 (54)	2.42*
Total									
Men	2,162 (84)	1,109 (89)	1.07*	1,980 (72)	2,169 (84)	1.17*	1,876 (53)	3,644 (76)	1.41*
Women	541 (84)	305 (88)	1.05	312 (69)	435 (78)	1.13*	242 (44)	551 (70)	1.56*

*$p < 0.05$, different from 1.00. Data presented are number of patients (8-year percent survival). CAD = coronary artery disease; LV = left ventricular; Rel = relative.

with a left ventricular score >9 and three-vessel disease, initial surgical management added 3.6 years of life for men and 3.7 years for women.

In general, mean survival within categories of risk was similar for men and women. Significant differences between men and women were observed in only four subgroups. These include patients <65 years old with two-vessel disease, a left ventricular score <10 and bypass surgery; patients <65 years

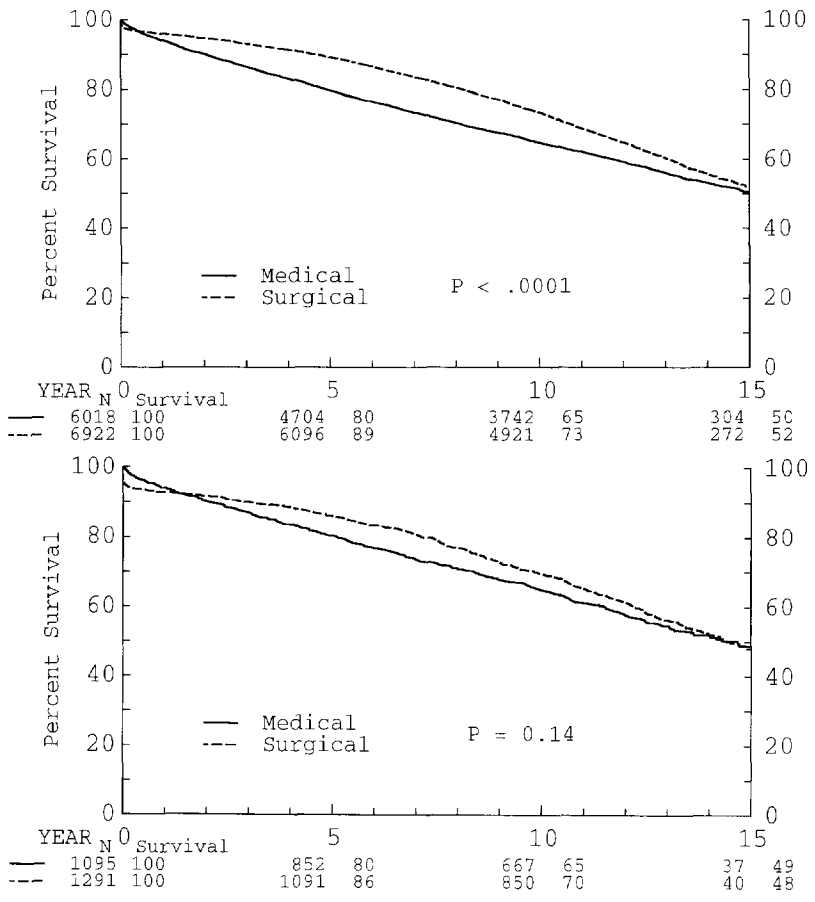

Figure 6. Percent survival of men (**top**) and women (**bottom**) treated with initial medical and surgical management.

Table 4. Mean Years of Survival Truncated at 14 Years and Differences for Men and Women With Initial Medical or Surgical Management

	Single-Vessel CAD			Double-Vessel CAD			Triple-Vessel CAD		
	Medical	Surgical	Diff	Medical	Surgical	Diff	Medical	Surgical	Diff
LV score <10									
Age <65 yr									
Men	12.6	12.7	0.1	12.0	12.3	0.3*	11.0	11.8	0.9*
Women	12.6	12.7	0.1	11.5	11.6	0.1	9.3	10.9	1.6*
Diff	0.0	0.1		0.5	0.7†		1.6†	0.9†	
Age ≥65 yr									
Men	10.3	11.0	0.7	10.2	11.3	1.0	8.2	10.1	1.8*
Women	11.7	10.9	−0.8	10.0	10.4	0.5	8.6	10.5	1.9*
Diff	−1.3	0.1		0.3	0.8		−0.4	−0.4	
LV score ≥10									
Age <65 yr									
Men	10.9	11.5	0.6	9.2	10.7	1.6*	6.9	10.1	3.1*
Women	10.6	9.7	−0.9	8.3	10.6	2.3*	6.4	8.5	2.1*
Diff	0.3	1.8		0.9	0.1		0.5	1.5†	
Age ≥65 yr									
Men	7.9	—	—	5.8	8.6	2.8*	4.6	8.2	3.6*
Women	8.8	—	—	7.2	9.4	2.2	4.0	7.8	3.7*
Diff	−0.9	—		−1.4	−0.9		0.6	0.5	

*$p < 0.05$, difference (Diff) between survival with initial medical and initial surgical management. †$p < 0.05$, difference between men and women. Abbreviations as in Table 3.

old with three-vessel disease, a left ventricular score <10 and either initial medical or surgical management; and patients <65 years old with three-vessel disease, a left ventricular score ≥10 and surgical management. These differences are not significant after correction for multiple comparisons by the Bonferroni method and should be interpreted cautiously because of the large number of statistical test results reported for these many subsets of patients.

Discussion

Rates of bypass surgery. A recent study (2) compared nearly 50,000 men and women who were hospitalized in Massachusetts and Maryland for acute myocardial infarction, unstable angina, angina pectoris, chronic ischemic heart disease or nonrespiratory chest pain in 1987. The investigators found that men had coronary bypass surgery at much higher rates than women. This difference persisted despite adjustment for a number of clinical characteristics, including age, congestive heart failure, diabetes and race. Unfortunately, because the investigators did not have information about coronary anatomy or status of left ventricular function, they would not have been able to come to any meaningful conclusion about the appropriate use of revascularization procedures in either the men or the women in their study population.

In the CASS registry, 39% of women and 11% of men had normal coronary arteries. If these patients, who had coronary arteriography for suspected ischemic coronary disease, had been included in our analysis of bypass surgery rates, it would have appeared that women were less often referred for surgical treatment. Even in our study population, which was restricted to those CASS patients appropriate for bypass surgery, if the adjustment used only clinical characteristics, the men appeared to have a higher rate of surgical intervention. With restriction to a population appropriate for bypass surgery and adjustment for both clinical and angiographic characteristics, the rates for men and women were not different. Thus, it is critically important for studies that compare rates of procedural utilization in men and women to adjust for both symptoms and severity of coronary artery disease and left ventricular dysfunction. Without simultaneous adjustment, rate estimates may be seriously biased.

Although we cannot judge the appropriateness of the use of coronary angiography in our study because this procedure was the starting point for enrollment in the CASS registry, there is no evidence that angiography was underutilized in women in the CASS registry because women were found to have significantly less coronary artery disease than men in the registry.

A study (7) of 4,707 men and 1,088 women with coronary artery disease who were enrolled in the Duke data registry showed referral rates to bypass surgery that were similar to ours. In the period 1969 to 1979, men and women who appeared to be equally likely to benefit from bypass surgery were referred in equal proportions. In the period 1980 to 1984, women with advanced coronary disease continued to be referred for coronary bypass surgery at the same rate as men. However, during the same period, women were less likely to be referred for bypass surgery than men if the procedure was expected to control symptoms but not improve survival. The reluctance to refer low risk women to bypass surgery in this period may have resulted from reports during this time of higher operative mortality for women (8–12).

Survival rates. Overall, the 15-year survival rates for men and women with initial medical management were similar. The

overall difference in 15-year survival rates for men and women with surgical management was approximately equal to the initial difference in operative mortality. When the Cox model was used to adjust for all covariates simultaneously, no significant differences in 15-year survival related to gender were found. This result agrees with previous studies of 5- and 10-year survival after bypass surgery that found no differences between men and women (9,12–16). In CASS as well as in other studies, the observed differences in operative mortality between men and women were in part due to the size of the patients and their coronary arteries rather than gender (12,17,18). The many improvements in anesthesia and surgical management that have occurred over the past 15 years have tended to decrease the differences in operative mortality between men and women (19). Thus, the estimates of early and long-term outcome for men and women described here need to be adjusted for the low surgical mortality currently experienced by both men and women.

The long-term outcome of these patients has also been influenced by improvements in medical management during the past 15 years (e.g., use of calcium channel blocking agents for the management of myocardial ischemia, improved management of unstable ischemic syndromes and marked advances in management of congestive heart failure). In addition, patients have benefited from the use of aspirin in recent years and the widespread use of effective lipid-lowering programs.

The introduction of coronary artery balloon angioplasty in the late 1970s and its wide application just a few years later have undoubtedly influenced the outcome of many patients similar to those in the present CASS registry analysis. It is possible that the use of angioplasty has had a greater influence in patients with initial medical versus initial surgical management. From the available CASS follow-up data, it was not possible to determine the relative role of angioplasty and bypass surgery in the outcome of patients in the present study.

Truncated mean survival. Between 8 and 10 years after bypass surgery, the slope of the surgical survival curve becomes steeper as a result of an increase in mortality during this period. This is consistent with previously published data (20,21) that showed this to be a period of increasing likelihood of closure of saphenous vein grafts. The difference in percent survival between the medical and surgical groups diminishes over time, so that at 14 to 15 years the survival rate is similar. To emphasize that an important difference in the shape of the survival curves exists even though survival rates at 14 years are similar, we compared the 14-year survival experiences by comparing the areas under the survival curves. This area represents the mean survival time truncated at 14 years, and the difference in mean survival times is an estimate of the number of years of life added by initial surgical treatment.

When mean survival time truncated at 14 years was compared for patients who were initially managed surgically or medically, the greatest benefit was seen in surgically managed patients with extensive coronary artery disease and decreased left ventricular function. For patients ≥65 years old with a left ventricular score ≥10 and three-vessel disease, the difference in mean survival time between initial surgical and medical management was 3.6 years for men and 3.7 years for women. For patients with single-vessel disease, the difference in mean survival time was only 0.1 to 0.7 years for men and 0.1 to 0.9 years for women. As was true in the comparison of 8-year survival times, there was little difference in benefit between men and women within most subgroups.

Conclusions. In a large population from the CASS registry, we compared the use of bypass surgery and survival over 15 years for men and women who were initially treated with and without bypass surgery. The rate of bypass utilization did not differ significantly between men and women, and there were few differences in their long-term survival. On average, survival of men and women treated with medical therapy was similar, and survival after 15 years for men and women with initial bypass surgery differed only by their difference in operative mortality. Overall, patients treated initially with bypass surgery survived longer, although the benefits were significant only in those patients who were at highest risk. The survival benefit of bypass surgery was similar for both men and women.

References

1. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993;329:247–56.
2. Ayanian JZ, Epstein AM. Differences in the use of procedures between men and women hospitalized for coronary heart disease. N Engl J Med 1991;325: 221–5.
3. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary disease. N Engl J Med 1991;325:226–30.
4. Principal Investigators of CASS and their associates. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS). Circulation 1981;63: Suppl I:I-1–81.
5. Irwin JO. The standard error of an estimate of expectation of life with special reference to expectation of tumorless life in experiments with mice. J Hyg 1949;47:188–9.
6. Kaplan EL, Meier P. Nonparametric observations from incomplete data. J Am Stat Assoc 1958;53:458–81.
7. Bickell NA, Pieper KS, Lee KL, et al. Referral patterns for coronary artery disease: gender bias or good clinical judgement? Ann Intern Med 1992;116: 791–7.
8. Bolooki H, Vargas A, Green R, Kaiser GA. Results of direct coronary artery surgery in women. J Thorac Cardiovasc Surg 1975;69:271–7.
9. Tyras DH, Barner HB, Kaiser GC, Codd JE, Laks H, Willman VL. Myocardial revascularization in women. Ann Thorac Surg 1978;25:449–53.
10. Douglas JS, King SB, Jones EL, Craver JM, Bradford JM, Hatcher CR. Reduced efficacy of coronary bypass surgery in women. Circulation 1981;64: Suppl II:II-11–6.
11. Kennedy JW, Kaiser GC, Fisher LF, et al. Clinical and angiographic predictors of operative mortality for the Collaborative Study in Coronary Artery Surgery (CASS). Circulation 1981;63:793–802.
12. Loop FD, Golding LR, Macmillan JP, Cosgrove JM, Lytle BW, Sheldon WC. Coronary artery surgery in women compared with men: analyses of risk and long-term results. J Am Coll Cardiol 1983;1:383–90.
13. Killen DA, Reed WA, Arnold M, McCallister BD, Bell HH. Coronary artery bypass in women: long-term survival. Ann Thorac Surg 1982;34:559–63.
14. Hall RJ, Elayda MA, Gray A, et al. Coronary artery bypass: long-term follow-up of 22,284 consecutive patients. Circulation 1983;68: Suppl II:II-20–5.
15. Myers WO, Davis K, Foster ED, Maynard C, Kaiser GC. Surgery survival in the Coronary Artery Surgery Study (CASS) registry. Ann Thorac Surg 1985;40:245–60.

16. Eaker ED, Kronmal R, Kennedy JW, Davis K. Comparison of the long-term, postsurgical survival of women and men in the Coronary Artery Surgery Study (CASS). Am Heart J 1989;117:71–81.
17. Fisher LD, Kennedy JW, Davis KB, et al. Association of sex, physical size, and operative mortality after coronary bypass in the Coronary Artery Surgery Study (CASS). J Thorac Cardiovasc Surg 1982;84:334–41.
18. O'Connor GT, Morton JR, Diehl MJ, et al. Differences between men and women in hospital mortality associated with coronary artery bypass surgery. Circulation 1993;88(1):2104–10.
19. Khan SS, Nessim S, Gray R, Czer LS, Chaux A, Matloff J. Increased mortality of women in coronary artery bypass surgery: evidence for referral bias. Ann Intern Med 1990;112:561–7.
20. Campeau L, Enjalbert M, Lesperance J, et al. Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. Circulation 1983;68: Suppl II:II-1–7.
21. Fitzgibbon GM, Leach AJ, Kafka HP, et al. Coronary bypass graft fate: long-term angiographic study. J Am Coll Cardiol 1991;17:1075–80.