Hormone replacement therapy is associated with improved survival in women undergoing coronary artery bypass grafting

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Objectives: The effect of hormone replacement therapy on cardiovascular events in postmenopausal women is controversial. We investigated the roles of sex and hormone replacement status in female patients undergoing coronary artery bypass grafting.

Methods: We reviewed the records of 4259 consecutive patients aged 55 years or older who underwent primary elective isolated coronary artery bypass at our hospital between May 1996 and September 2001.

Results: Female sex with hormone replacement therapy was an independent predictor of decreased mortality, regardless of age. Mortality was 6.7% (61/905) for women not receiving hormone replacement therapy, 2.3% (6/256) for hormone replacement therapy recipients, and 2.7% (82/3098) for men ($P < .01$ for all comparisons). Of the characteristics examined, multivariate analysis indicated that independent predictors of mortality were advanced age, previous congestive heart failure, class IV angina, and female sex without hormone replacement ($P < .005$). Independent predictors of survival included use of an internal thoracic artery graft and white ethnicity. There were no significant intergroup differences in the incidence of nonfatal, morbid postoperative events.

Conclusions: Postmenopausal women undergoing coronary artery bypass had a significantly improved in-hospital survival if they had been receiving hormone replacement therapy. The improved survival might be related to one or more of the numerous cardiovascular effects of estrogen that are considered beneficial. A prospective randomized trial is needed to validate the observation that hormone replacement therapy is protective in this setting.

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Among patients undergoing coronary artery bypass grafting (CABG), the in-hospital mortality has consistently been higher in women than in men.^{1,2} Explanations for this difference have focused primarily on the more frequent comorbidity that is predictive of a poor outcome in women. In some studies statistical adjustment of mortality for risk-factor profiles eliminated female sex as an independent predictor.^{1,3,4} In the largest CABG database, however, female sex remained an independent predictor, despite risk-factor adjustment.²

None of these studies explored the possible role of hormone replacement therapy (HRT) in perioperative mortality. Such therapy is not recommended for secondary prevention of cardiovascular disease and is controversial, even for primary prevention.⁵⁻⁷ Nevertheless, investigators have described numerous cardiovascular effects of estrogen that are considered beneficial,⁸ including attenuation of adverse responses to endoluminal vascular trauma.⁹ Limited clinical studies suggest that HRT in postmenopausal women favorably affects long-term outcome after the endolu-

minimal trauma of coronary angioplasty and CABG.¹⁰⁻¹² Shackelford and colleagues¹³ recently assessed the mortality after isolated CABG in 734 consecutive women, of whom 102 had received HRT preoperatively. On univariate, but not multivariate, analysis, the in-hospital mortality was significantly lower in the women who received HRT (2.7% vs 7.4%). The present study was undertaken to obtain additional data regarding the attractive hypothesis that HRT improves the in-hospital outcomes of cardiovascular surgical procedures that induce endoluminal vascular injury.

Methods

This retrospective analysis was performed on a comprehensive, prospectively collected database that included all patients treated at the Texas Heart Institute since 1993. (Completed patient charts are routinely abstracted, and data relating to risk factors and outcomes are entered into the database.) This study included 4259 consecutive men and women aged 55 years or older who underwent primary elective CABG with cardiopulmonary bypass between May 1996 and September 2001, without concomitant procedures, such as valve or ventricular aneurysm repair. The 55-year cut-off point for postmenopausal status is widely used.^{12,14-16} Female patients were classified as receiving HRT if oral or transdermal estrogen replacement or combined estrogen-progesterone replacement therapy was recorded in the physician's notes or the nurse's patient-admission assessment, which includes a list of current medications. All other patients were classified as not receiving HRT. For female patients receiving HRT, the first two thirds (172/256) of the hospital records were rechecked to verify documentation of HRT status at the time of admission; no errors were found. Duration of HRT was not recorded in the database. In no instance, however, was HRT initiated by the admitting physician.

All analyses involved 3 groups: women not receiving HRT, women receiving HRT, and men. These were the primary predictor variables, with women without HRT serving as the reference group. Other potential preoperative predictor variables included age, body mass index, race (white vs nonwhite), preoperative ejection fraction, number of diseased coronary vessels, diabetes (with or without insulin dependence), history of congestive heart failure, unstable angina, previous myocardial infarction, tobacco use, peripheral vascular disease with or without intervention, hypertension, chronic obstructive pulmonary disease or asthma, or dialysis-dependent renal failure. The potential influence of preoperative concurrent therapy, including angiotensin-converting enzyme inhibitors, calcium-channel blockers, β -blockers, antihyperlipidemic agents, and aspirin, was also included in the analysis. Potential perioperative predictor variables included the number of vessels bypassed and use of an internal thoracic artery (ITA) graft.

The primary outcome variable was in-hospital mortality. Secondary outcome variables included major perioperative morbidity, such as myocardial infarction, use of an intra-aortic balloon pump, stroke, new onset of renal failure necessitating dialysis, postoperative infection, respiratory insufficiency (when diagnosed by a pulmonary specialist), postoperative bleeding necessitating re-exploration, and thromboembolic events (deep venous thromboembolism or pulmonary embolism). Univariate associations between

potential predictors and outcome were assessed by means of χ^2 analysis, followed by stepwise logistic modeling, which examined all significant predictors ($P = .10$) for all groups.

Results

Of the 4259 patients in this study, 1161 were women, of whom 256 (22.0%) were receiving HRT at hospital admission. This incidence of HRT is similar to the 20% estrogen-use rate reported by the National Center for Health Statistics.¹⁷ Of the 256 HRT recipients, 85% took conjugated estrogen (Premarin) or estradiol (Estrace or Estraderm) only. The remainder took a combination of conjugated estrogen and medroxyprogesterone acetate (Prempro, Premphase, or Premarin plus Provera).

The in-hospital mortality for all patients was 3.5%. For women not receiving HRT, the mortality was 6.7% compared with 2.3% for women receiving HRT and 2.7% for men ($P = .008$ compared with HRT recipients and $P < .0001$ compared with men by means of univariate analysis). Multivariate analysis confirmed that female sex without HRT was an independent predictor of increased in-hospital mortality ($P < .005$).

Preoperative patient characteristics, intraoperative data, and length of hospital stay for the 3 groups were compared (Table 1). Compared with women receiving HRT, the women not receiving HRT were older (by 2.4 years, $P < .0001$), were more likely to be nonwhite ($P < .0001$), were more likely to have a history of diabetes ($P < .007$) and congestive heart failure ($P = .002$), had more diseased vessels ($P = .0002$), and had more vessels bypassed ($P = .002$). Women receiving HRT were more often smokers ($P = .04$), had a higher incidence of hypertension ($P = .04$), and had more frequent use of an ITA graft ($P = .003$).

Multivariate analysis for independent predictors of mortality indicated that female sex without HRT significantly predicted higher in-hospital mortality (Table 2). Other independent predictors were advanced age, history of congestive heart failure, and class IV angina. Independent predictors of survival included use of an ITA graft and white race (Table 2).

The mortality of all the women in this study was examined in terms of precipitating and ultimate causes to identify possible differences in patterns of mortality between women receiving and not receiving HRT. The result was unrewarding because of the small number of deaths in the HRT group ($n = 6$). In both groups approximately 50% of the deaths were primarily cardiac (ie, related to cardiogenic shock, myocardial infarction, arrhythmia, or congestive heart failure), and 13% were primarily related to the central nervous system (stroke and encephalopathy). Other causes of death included respiratory failure, renal failure, gastrointestinal complication, hemorrhage, sepsis, pulmonary embolus, and multiorgan system failure. The pattern of postoperative morbidity among the 3 groups was similarly compared

TABLE 1. Patient characteristics

Characteristics	Women receiving HRT (n = 256)	Women not receiving HRT (n = 905)	Men (n = 3098)
Age (y)	68.0 ± 7.8	70.4 ± 8.0†	67.1 ± 7.7
Body mass index (kg/m ²)	27.6 ± 5.5	28.1 ± 6.2	27.9 ± 5.0
White ethnicity (%)	85.2	69.8‡	72.2‡
Diabetes (%)	29.3	38.6†	31.1
Ejection fraction (%)	53.0 ± 11.8	51.4 ± 14.3	48.7 ± 13.4†
NYHA class IV angina (%)	13.3	16.0	11.3§
No. of vessels diseased*	1.7 ± 0.9	1.9 ± 1.0	2.1 ± 0.9
History of:			
Tobacco use (%)*	40.0	33.0	53.2
Congestive heart failure (%)	20.7	30.8†	19.0
Previous MI (%)	35.9	39.1	40.5
Hypertension (%)*	84.8	79.1	70.2
Peripheral vascular disease (%)	24.2	28.5	19.5§
Renal failure (%)	0.39	0.11	0.23
COPD (%)	10.9	12.4	10.3
Preoperative IABP (%)	1.2	1.1	1.2
Use of an ITA graft (%)*	84.4	75.7	89.7
Duration of CPB (min)	58.1 ± 32.9	62.5 ± 36.2	64.5 ± 32.7‡
No. of vessels bypassed*	2.7 ± 1.0	2.9 ± 1.1	3.3 ± 1.1
Postoperative hospital stay (d)	9.8 ± 7.7	10.2 ± 7.7	9.4 ± 8.7§

Values are presented as means ± SD. NYHA, New York Heart Association; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass.

*P < .05 for all comparisons among groups.

†P < .05 versus both other groups.

‡P < .05 versus women receiving HRT.

§P < .05 versus women not receiving HRT.

(Table 3). There were no significant differences in morbidity related to HRT.

Discussion

Women undergoing CABG consistently have a higher operative mortality than men,^{1,2} but there is no agreement as to whether female sex, per se, is an independent risk factor. In several reports that have shown a higher in-hospital mortality in women, investigators have used various statistical models to adjust for body surface area, coronary artery size, or risk-factor profile.^{1,3,4} With such adjustments, the male-female difference tended to lose significance. However, in the largest database, which included 97,153 women and 247,760 men who underwent isolated CABG between 1994 and 1996, women still had a significantly higher operative mortality (4.5% vs 2.6%),² even when confounding risk factors were adjusted. This observation was reaffirmed in a reanalysis of these data.¹⁸ In none of the studies cited above was HRT examined as a predictor of mortality. Our data support female sex as an independent predictor of mortality and further suggest that HRT reduces risk in women to that in men.

The effect of HRT on the cardiovascular system is not clear.^{5-8,19} A large number of observational studies suggested that HRT offers substantial cardiovascular bene-

TABLE 2. Multivariate preoperative predictors of mortality or survival after CABG

	OR	95% CI	P value
Predictors of mortality			
Age ≥75 y	4.0	2.3-6.8	<.0001
Age 65-75 y	2.5	1.5-4.3	.0004
Previous congestive heart failure	3.4	2.4-4.9	<.0001
Class IV angina	1.7	1.1-2.7	.02
Female sex without HRT	1.7	1.2-2.5	.004
Predictors of survival			
Use of an ITA graft	0.6	0.4-0.9	.006
White race	0.6	0.4-0.8	.003

Only predictor variables significant in the multivariate analysis are included (see the "Methods" section for list of all variables analyzed). OR, Odds ratio; CI, confidence interval.

fits.²⁰⁻²² However, the results of large, prospective, randomized controlled clinical trials designed to study the effects of HRT in women with or without known coronary artery disease—the Heart and Estrogen/Progestin Replacement Study,¹⁴ the Estrogen Replacement and Atherosclerosis trial,¹⁵ and the Women's Health Initiative study⁷—showed no significant benefit and raised the possibility of short-term increases in risk. For secondary prevention of cardiovascu-

TABLE 3. Morbidity after CABG

Complications	Women receiving HRT (n = 256)	Women not receiving HRT (n = 905)	Men (n = 3098)
Myocardial infarction	11 (4.3%)	29 (3.2%)	101 (3.3%)
Intra-aortic balloon pump	4 (1.6%)	5 (0.6%)	21 (0.7%)
Stroke	8 (3.1%)	44 (4.9%)	112 (3.6%)
Renal failure	2 (0.8%)	21 (2.3%)	43 (1.4%)
Any infection	19 (7.4%)	85 (9.4%)	208 (6.7%)*
Respiratory failure	30 (11.7%)	97 (10.7%)	310 (10.0%)
Postoperative reoperation for bleeding (%)	10 (3.9%)	30 (3.3%)	138 (4.5%)
Thromboembolic event	1 (0.4%)	8 (0.9%)	8 (0.7%)

* $P < .05$ versus women not receiving HRT.

lar events, the latest American Heart Association recommendations state that combinations of estrogen plus progesterone should not be initiated for this purpose.^{5,7} Definitive evidence regarding the benefits and risks of estrogen administered alone (without progesterone) for primary prevention of cardiovascular disease should emerge from the ongoing branch of the Women's Health Initiative trial involving women who had a hysterectomy, to be completed in 2005.⁷

It is possible that the benefits of HRT are most evident in the presence of vascular injury, as noted in numerous laboratory studies.^{9,23-28} It has been clearly shown that endothelial cells and vascular smooth muscle cells possess estrogen receptors and that estrogen modulates the vascular responses to numerous endogenous hormones. In animal models of endoluminal injury of normal blood vessels, estrogen inhibits the hyperproliferation resulting from activation of adventitial cells and their migration toward the lumen.²⁹ In the rat model with a balloon-injured common carotid artery, Oparil and colleagues^{9,23-28} showed that estrogen inhibited neointima formation by affecting all 3 layers of the vascular wall, inhibiting medial smooth muscle cell migration and proliferation, stimulating regrowth of the endothelium, and inhibiting adventitial-cell migration into neointima. Other data suggest women receiving HRT have greater endogenous fibrinolysis³⁰ and that estrogen modifies the inflammatory response to reperfusion injury in animals.^{31,32} It is not at all clear which aspect of estrogen's action might mediate a benefit in the presence of vascular injury.

Some clinical data support the benefits of estrogen in the presence of vascular injury. Shlipak and colleagues¹⁶ studied 114,724 women aged 55 years or older with confirmed myocardial infarction participating in the National Registry of Myocardial Infarction 3. At hospitalization, 7353 (6.4%) reported current use of HRT. Unadjusted mortality was 7.4% in users of HRT and 16.2% in nonusers (odds ratio, 0.41; confidence interval, 0.36-0.43). O'Keefe and coauthors¹⁰ retrospectively studied 337 postmenopausal women undergoing elective percutaneous transluminal coronary an-

gioplasty, of whom 137 were consecutive women receiving long-term estrogen therapy at the time of percutaneous transluminal coronary angioplasty. The control group comprised 200 nonusers of estrogen who were computer matched to the estrogen group. The 7-year survival rate was significantly better in the estrogen group (93% vs 75%, $P = .001$), and the cardiovascular event rate was significantly lower in the estrogen group.¹⁰ Also, Khan and associates¹¹ studied 129 women who underwent stenting of a single coronary artery. Estrogen treatment significantly reduced the need for repeat-target lesion revascularization (14/49 HRT users vs 30/56 nonusers). Sullivan and coworkers¹² studied 1098 postmenopausal women undergoing CABG. Although only 92 (8.4%) women were receiving HRT at the time of CABG, they had a 5-year survival rate of 98.8% compared with 82.3% for non-HRT users and a 10-year survival rate of 81.4% versus 65.1%, respectively. In a multivariate analysis of long-term survival after CABG, use of HRT remained a significant predictor of survival. More recently, Shackelford and colleagues¹³ retrospectively studied 734 consecutive postmenopausal women undergoing isolated CABG from 1992 to 1997, of whom 102 (13.9%) received estrogen. Univariate analysis showed that the perioperative mortality was significantly lower in the women receiving HRT (2.7% vs 7.4%), but stepwise logistic regression failed to confirm the significance of HRT use. Our mortality data from a larger population are strikingly similar to these. In our data, however, female sex with HRT was a significant independent predictor of a lower in-hospital mortality after isolated CABG.

Our study has several limitations apart from those inherent in a retrospective single-institution analysis. HRT data were not routinely recorded before May 1996. Neither were specific doses recorded. Despite a large sample of 4259 patients, only 27.3% were women, and of these, only 22% were receiving HRT. These small numbers decreased the statistical power for detecting differences in patterns of outcome that might have provided clues to the mechanism of benefit by HRT. A further limitation common to observational studies such as this one is that the apparent benefit

of HRT could be the result of selection bias not apparent from the characteristics we have recorded. Our group of women receiving HRT compared with the group not receiving HRT were 2.4 years younger, were more often of white ethnicity, had less diabetes, had less congestive heart failure, had fewer diseased vessels, and were more frequently given an ITA graft. Conversely, they were more often smokers, had more hypertension, and had fewer vessels bypassed. Even though multivariate analysis identified age, congestive heart failure, class IV angina, white race, and use of an ITA in addition to HRT as independent predictors of mortality versus survival, a selection bias could account for the apparent benefit of HRT. These limitations could be further resolved by a prospective multi-institutional study designed to acquire larger numbers of female patients with more balanced comorbidity and additional characteristics recorded. A possible reduction in the CABG mortality and better outcome after angioplasty warrants such an effort.

After CABG in patients aged 55 years or older, women receiving HRT had a significantly lower in-hospital mortality than did women not receiving HRT. In fact, mortality after CABG in female HRT recipients was similar to that of men. We postulate that one or more of the cardiovascular actions of estrogen might benefit the coronary response to endoluminal injury of CABG. Randomized prospective trials are required to address the broader issues of HRT and cardiovascular health.

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