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Relation Between Estrogen Replacement Therapy and Restenosis After Percutaneous Coronary Interventions

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Objectives. **We attempted to determine the relation between estrogen replacement therapy and the rate of restenosis after coronary angioplasty and atherectomy.**

Background. **Although estrogen replacement therapy in women has been associated with a reduction in cardiovascular events and improvement in endothelial function, no study has examined whether estrogen reduces restenosis rates after percutaneous coronary interventions.**

Methods. **A total of 204 women enrolled in the Coronary Angioplasty Versus Excisional Atherectomy Trial with angiographic follow-up were contacted, and their menopausal and estrogen replacement status was determined. Late loss in minimal lumen diameter, late loss index, minimal lumen diameter, rate of restenosis >50% and actual percent of stenosis were compared in estrogen users and nonusers by quantitative coronary angiography at 6-month follow-up.**

Results. **Late loss in minimal lumen diameter was significantly less in women using estrogen than in nonusers (−0.13 vs. −0.46 mm, p = 0.01). A regression analysis of the determinants of late loss in minimal lumen diameter revealed that estrogen use was the single most important predictor of subsequent late loss (F = 13.38, p = 0.0006). Formal testing revealed a highly significant interaction between the use of estrogen and intervention (angioplasty or atherectomy). Women undergoing atherectomy who received estrogen had a significantly lower late loss index (0.06 vs. −0.63, p = 0.002), less late loss (0.06 vs. −0.61 mm, p = 0.0006), larger minimal lumen diameter (p = 0.044) and lower restenosis rates (p = 0.038 for >50% stenosis) than those not using estrogen. In contrast, estrogen had minimal effects on restenosis end points after angioplasty.**

Conclusions. **This study demonstrates the potential for estrogen replacement therapy to reduce angiographic measures of restenosis in postmenopausal women after coronary intervention, particularly in those undergoing atherectomy.**

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Restenosis remains a major limitation to the long-term benefit of percutaneous transluminal coronary angioplasty and directional coronary atherectomy. Several clinical studies (1–4) have reported the rate of angiographically defined late restenosis after angioplasty to be between 30% and 50%. Despite multiple clinical trials evaluating numerous pharmacologic agents (5–12), few drugs to date have shown any potential to significantly reduce the rate of restenosis. However, none of these previous studies examined the value of estrogen replacement therapy in decreasing the rate of restenosis in selected patients.

Extensive observational data exist detailing an association between estrogen replacement therapy and a reduction in cardiovascular disease in postmenopausal women. Primarily epidemiologic studies have demonstrated a 50% reduction in the relative risk of cardiovascular events in postmenopausal women taking estrogen compared with those not receiving estrogen (13,14). In addition, recent studies (15–27) suggest that estrogen may reduce the progression of existing coronary artery disease in postmenopausal women, favorably modulate the vascular biology of atherosclerotic coronary arteries and limit the proliferation of vascular smooth muscle after endothelial injury.

Given these potential favorable effects of estrogen on coronary vascular biology, we hypothesized that estrogen replacement therapy in postmenopausal women would reduce angiographic measures of restenosis and improve functional status and clinical outcomes after percutaneous coronary interventions. To test this hypothesis, we examined the impact of

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estrogen on restenosis in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I).

Methods

Study patients. A detailed description of the trial has been published previously (28). Between August 1991 and April 1992, 275 women who had given written informed consent in the United States and Europe were randomized to either angioplasty or atherectomy at 35 sites participating in CAVEAT I. Eligibility criteria included the presence of symptomatic ischemic heart disease amenable to treatment with either angioplasty or atherectomy, diseased native coronary vessels with no previous coronary interventions, and ≥60% stenosis on visual assessment. Patients with multivessel disease were eligible, but a single target vessel suitable for either angioplasty or atherectomy was specified before coronary intervention. Although the study protocol considered a residual stenosis of <20% optimal, a reduction of lesions to ≤50% diameter stenosis was considered a successful procedure.

For the current study, we included only the 254 women randomized within 32 hospitals participating in CAVEAT I within the United States in order to ensure a consistent method of data collection and subsequent verification.

Angiographic analysis. As part of CAVEAT I, the procedural details of angioplasty and atherectomy and the results of cardiac catheterization were collected prospectively. The cineangiograms were quantitatively analyzed at the Cleveland Clinic Foundation by technicians who had no knowledge of intervention assignments or outcome data (28). When multiple views of the target lesion were available, the most severe hemiaxial view of the stenosis without foreshortening was selected for analysis. End-diastolic cine frames from orthogonal views were digitized with a cine-video converter and a computer-assisted edge detection algorithm (29).

A total of 204 (80%) of 254 eligible women in CAVEAT I had angiographic follow-up within 6 months. If a patient underwent repeat catheterization before the scheduled procedure because of a change in clinical status, that angiogram was used to obtain follow-up data. The reasons for failure to obtain angiographic follow-up included refusal to undergo repeat catheterization (27 patients), coronary artery bypass surgery (n = 10), death (n = 5), intercurrent illness (n = 2), lost to follow-up (n = 5) and withdrawal from the study (n = 1). Of the 50 women without angiographic follow-up, 6 were using estrogen replacement therapy. Of these six, three subsequently had coronary artery bypass surgery and all three refused to undergo repeat catheterization.

End points. The primary angiographic end point for the current study was prospectively defined as the mean difference in minimal lumen diameter between the 6-month angiogram and the postprocedure angiogram (late loss) as determined by quantitative angiography. This end point has been used in several previous angiographic restenosis trials (4). Secondary angiographic end points included 1) the late loss index (late loss divided by immediate gain in minimal lumen diameter), 2) minimal lumen diameter at follow-up, 3) dichotomous rate of restenosis (>50% stenosis), and 4) actual percent stenosis at 6-month follow-up.

The clinical end points collected at 1 year included all-cause mortality, myocardial infarction, coronary artery bypass surgery, repeat cardiac catheterization and exertional angina class (defined by Canadian Cardiovascular Society class). A composite 1-year clinical end point was also defined as death, myocardial infarction, coronary artery bypass surgery and nonsurgical coronary intervention in the target artery.

Determination of estrogen replacement use. A total of 246 (97%) of 254 women previously enrolled in CAVEAT I from the United States were contacted between March and May 1995. Menopausal status and estrogen replacement status at the time of randomization and at the 6-month and 1-year follow-up were collected by structured telephone interview by one investigator who had no knowledge of outcome data. Of 254 women, 7 could not be contacted by telephone but subsequently responded to a mailed questionnaire. A total of eight women could not be contacted by telephone or mailed questionnaire (six of the eight died after randomization and two were lost to follow-up). For the six women who died after randomization, both medical record review and physician contact were used to determine estrogen replacement status. Nine women were determined to be premenopausal at the time of percutaneous coronary intervention by interview or questionnaire and were removed from all subsequent analyses. For the purpose of the study, positive estrogen replacement status was specified as unopposed estrogen or combined estrogen/progestin regimens initiated before the time of initial coronary intervention and used continuously through both 6-month and 1-year follow-up. Any patient who discontinued estrogen replacement therapy before angiographic or 1-year follow-up was considered to be in the nonestrogen replacement group (four patients). Positive estrogen replacement status was verified for all respondents by a combination of medical record review and prescribing physician contact.

Statistical analysis. Baseline characteristics of the estrogen replacement and the nonestrogen replacement groups are presented as medians with interquartile ranges for continuous variables and percentages for discrete variables. Selected baseline characteristics and clinical and angiographic outcomes were compared between groups by using the Wilcoxon rank-sum test for continuous variables and the Mantel-Haenzel chi-square test or Fisher exact test, where appropriate, for discrete variables. Kaplan-Meier curves were used to compare the probability of clinical outcomes for the 1-year follow-up period by estrogen replacement status. The two study groups were compared with respect to clinical outcomes and composite end point at 1 year with use of the log rank test. The Fisher exact test was also used to evaluate angina class at 1 year for both groups. Because patients underwent 1-year follow-up at varying times, the angina class used as the 1-year follow-up value was obtained between 8 and 16 months after randomization. All tests of significance were two-tailed.

Multiple linear regression was used to assess the association

between late loss in minimal lumen diameter at follow-up and estrogen use after adjusting for multiple baseline clinical factors known to affect the rate of restenosis. The independent variables considered in this model included patient age, diabetes mellitus, current smoking, hypertension, high density lipoprotein level, unstable angina, vessel diameter, preprocedure minimal lumen diameter, presence of a lesion in the left anterior descending coronary artery, type of coronary intervention (angioplasty or atherectomy), and use or nonuse of estrogen replacement. To investigate whether the effect of estrogen use on restenosis differed between patients who underwent directional coronary atherectomy versus those who had coronary angioplasty, we included a formal test for interaction between coronary intervention and estrogen use. As this interaction term (coronary intervention × estrogen use) was significant ($p = 0.005$), we stratified our angiographic outcomes by the type of coronary intervention received. In addition, unadjusted univariable analyses of the independent variables considered in the multivariable model were used to evaluate correlates of late loss in minimal lumen diameter.

Results

Of 243 women, 47 (19%) were using continuous unopposed estrogen or combined estrogen/progestin regimens before coronary intervention through the time of 1-year clinical follow-up. Thirty-eight (81%) of these women were taking unopposed conjugated equine estrogen (32 patients), estradiol (n = 4) or estrone (n = 2). Nine patients reported use of combined estrogen/progestin regimens. No woman reported initiating estrogen replacement therapy after coronary intervention or 6-month angiographic follow-up.

Characteristics of the patients. The baseline characteristics of the estrogen replacement users and nonusers are shown in Table 1. Women receiving estrogen replacement therapy were significantly younger, more likely to be smokers and more often had a positive family history of coronary artery disease. In addition, women using estrogen had significantly higher levels of high density lipoprotein and lower baseline rates of classes III and IV angina before coronary intervention. The two groups were similar with respect to factors associated with an increased risk of restenosis, including unstable angina and lesion location in the left anterior descending artery.

Immediate angiographic outcomes. The baseline angiographic data and immediate interventional outcomes in estrogen users and nonusers are displayed in Table 2. Percent stenosis before and after intervention was similar between estrogen users and nonusers. Women using estrogen replacement had smaller minimal lumen diameters before and after intervention ($p = 0.05$ and 0.055, respectively). However, the immediate gain for both estrogen users and nonusers varied little (0.93 vs. 0.97 mm, $p = 0.71$). Likewise, immediate success rate (defined as ≤50% stenosis by quantitative angiography) was high in both estrogen users and nonusers (89% vs. 89%, $p = 1.0$).

Table 1. Baseline Clinical and Angiographic Characteristics

	Estrogen Users (n = 47)	Estrogen Nonusers (n = 196)	p Value
Age (yr)	60 (52, 67)	64 (57, 71)	0.003
Diabetes	25%	33%	0.31
Current smoker	30%	17%	0.054
Hypertension	62%	63%	0.89
Cholesterol (mg/dl)	233 (209, 261)	226 (199, 253)	0.34
High density lipoprotein (mg/dl)	54 (41, 60)	39 (32, 50)	0.002
Family history of CAD	61%	38%	0.005
Prior history of myocardial infarction	28%	41%	0.084
Comorbid disease*	38%	41%	0.70
CCS angina class III or IV	57%	73%	0.032
Unstable angina	81%	84%	0.64
Target vessel = LAD	54%	51%	0.71

*Comorbid disease includes renal insufficiency (creatinine >1.5 mg/dl), malignancy, chronic lung disease, rheumatologic disease, alcohol abuse, depression, physician-diagnosed obesity, gastrointestinal bleeding and cirrhosis. Data presented are median value (25th, 75th percentile) or percent of patient group. CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; LAD = left anterior descending coronary artery.

Six-month follow-up. The angiographic follow-up data are displayed in Table 3 and Figure 1. The primary end point, the median late loss in minimal lumen diameter, was significantly lower in women using estrogen than in nonusers (−0.13 vs. −0.46 mm, $p = 0.01$). In fact, univariable analysis of potential risk factors of restenosis revealed that estrogen use was the strongest predictor of late loss in minimal lumen diameter ($F = 10.56$, $p = 0.001$). In a multivariable analysis, the reduction in late loss remained significant after adjusting for potential risk factors for restenosis, including age, diabetes, current smoking, hypertension, high density lipoprotein level, unstable angina, vessel diameter, preprocedure minimal lumen diameter, presence of a lesion in the left anterior descending artery and type of coronary intervention (angioplasty or atherectomy). Multivariable regression analysis also found that estrogen use was the single most important predictor of subsequent late loss ($F = 13.38$, $p = 0.0006$). The only other

Table 2. Immediate Angiographic Outcomes

	Estrogen Users (n = 47)	Estrogen Nonusers (n = 196)	p Value
Preprocedure stenosis (%)	73 (63, 79)	72 (62, 78)	0.38
Postprocedure stenosis (%)	36 (29, 43)	35 (29, 45)	0.81
Preprocedure MLD (mm)	0.67 (0.48, 1.03)	0.82 (0.62, 1.06)	0.05
Postprocedure MLD (mm)	1.64 (1.42, 1.78)	1.75 (1.48, 2.06)	0.055
Acute gain (mm)*	0.93 (0.56, 1.19)	0.97 (0.62, 1.24)	0.71
Success rate†	89%	89%	1.0

*Defined as postprocedure minimal lumen diameter minus preprocedure minimal lumen diameter. †Rate of reduction of stenosis to ≤50% as assessed by quantitative angiography. Data presented are median value (25th, 75th percentile) or percent of patient group. MLD = minimal lumen diameter.

Table 3. Angiographic Outcomes at Six-Month Follow-Up

	Estrogen Users (n = 41)	Estrogen Nonusers (n = 163)	p Value
Late loss (mm)*	−0.13 (−0.78, 0.12)	−0.46 (−0.80, −0.12)	0.01
Late loss index†	−0.136 (0.71, 0.17)	−0.52 (−0.92, −0.18)	0.005
Minimal lumen diameter (mm)	1.37 (0.85, 1.80)	1.24 (0.89, 1.68)	0.55
Rate of restenosis‡	41%	50%	0.26
Percent stenosis (%)§	48 (31, 60)	55 (38, 67)	0.18
Vessel caliber (mm)	2.5 (2.2, 3.0)	2.7 (2.4, 3.0)	0.03

*Defined as 6-month follow-up minimal lumen diameter minus postprocedure minimal lumen diameter. †Late loss divided by acute gain in minimal lumen diameter. ‡>50% stenosis after an initially successful procedure. §Actual percent stenosis. Data presented are median value (25th, 75th percentile) or percent of patient group.

clinical factors found to significantly affect late loss were the intervention ($F = 8.08$, $p = 0.005$) and the interaction between the intervention and estrogen use ($F = 7.22$, $p = 0.008$).

Although the late loss index varied significantly between estrogen users and nonusers (−0.126 vs. −0.522, $p = 0.005$), no significant differences existed when the other secondary angiographic end points were analyzed. However, similar trends toward improved outcomes were noted among estrogen users (Table 3). Despite having smaller lumen diameters before and after intervention, women using estrogen had a slightly larger median minimal lumen diameter at 6-month follow-up than did nonusers (1.37 vs. 1.24 mm, $p = 0.55$). In addition, estrogen users tended to have a lower restenosis rate (>50% stenosis) than did nonusers when the dichotomous end point was used (41% vs. 50%, $p = 0.26$).

As noted before, a predetermined analysis included investigating whether the effects of estrogen replacement therapy on angiographic restenosis varied between those who underwent atherectomy and those treated with conventional angioplasty. The testing for an interaction between coronary intervention and estrogen replacement use confirmed the existence of this differential effect. Therefore Table 4 and Figures 2 and 3 display angiographic outcomes by coronary intervention and estrogen status. The median late loss in estrogen users undergoing atherectomy was 0.06 mm compared with −0.61 mm in nonusers ($p = 0.0006$). Likewise, the late loss index varied significantly between estrogen users and nonusers treated with atherectomy (0.06 vs. −0.63, $p = 0.002$). The median minimal lumen diameter in estrogen users undergoing atherectomy was larger than in nonusers (1.63 vs. 1.15 mm, $p = 0.044$), and the dichotomous restenosis rate (>50% stenosis) in estrogen users undergoing atherectomy was 27% compared with 57% in nonusers ($p = 0.038$). Little difference in minimal lumen diameter existed between estrogen users and nonusers who underwent angioplasty (1.26 vs. 1.32 mm, $p = 0.34$). Similarly, the dichotomous restenosis rates were not significantly different between estrogen users and nonusers who received angioplasty.

Clinical outcomes. The clinical events and cumulative clinical outcome at 1-year follow-up are shown in Table 5. Six patients (3%) in the nonestrogen replacement group died within 365 days of coronary intervention. No deaths occurred in the estrogen replacement group. The rates of myocardial infarction, coronary artery bypass surgery and need for coronary intervention were slightly lower in estrogen users than in nonusers. The composite clinical end point (death, myocardial infarction, coronary artery bypass surgery and nonsurgical coronary intervention in the target artery) was similar between estrogen users and nonusers (15 events [31.9%] vs. 71 [35.5%], $p = 0.75$). However, the number of patients who were classified as having class II, III or IV angina at follow-up demonstrated a trend toward less severe angina in estrogen users (5 patients [10.6%] vs. 31 [21.3%], $p = 0.29$).

Discussion

Restenosis remains a significant limitation for patients undergoing percutaneous coronary intervention, with 30% to

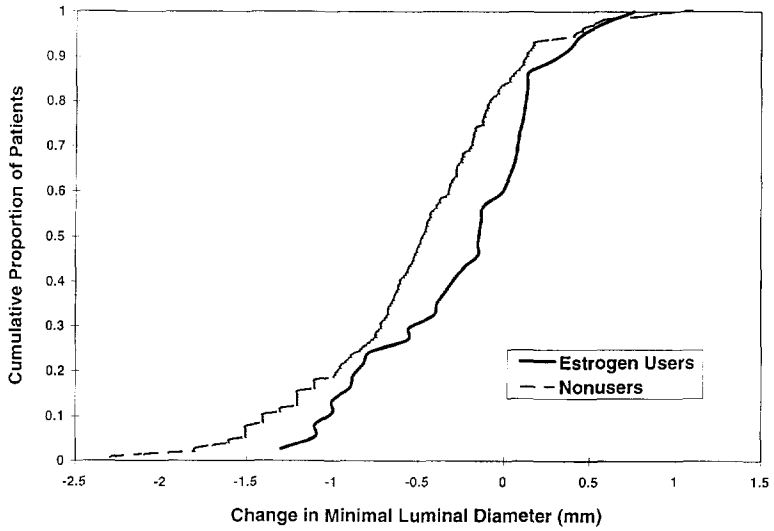

Figure 1. Cumulative frequency distribution of late loss in minimal lumen diameter of the target lesion in estrogen users and nonusers undergoing angioplasty and atherectomy.

Table 4. Angiographic Outcomes at Six-Month Follow-Up According to Intervention Assignment

	Atherectomy			Angioplasty		
	Estrogen Users (n = 18)	Estrogen Nonusers (n = 79)	p Value	Estrogen Users (n = 23)	Estrogen Nonusers (n = 84)	p Value
Late loss (mm)*	0.06 (−0.15, 0.29)	−0.61 (−0.99, −0.23)	0.0006	−0.29 (−0.82, 0.09)	−0.39 (−0.66, −0.08)	0.77
Late loss index†	0.06 (−0.20, 0.34)	−0.63 (−0.97, −0.21)	0.002	−0.40 (−0.81, 0.17)	−0.44 (−0.84, −0.08)	0.40
Minimal lumen diameter (mm)	1.63 (0.83, 1.99)	1.15 (0.88, 1.49)	0.044	1.26 (0.88, 1.53)	1.32 (0.92, 1.72)	0.34
Rate of restenosis‡	27%	57%	0.038	48%	50%	0.69
Percent stenosis (%)§	31 (20, 59)	59 (38, 69)	0.01	51 (42, 66)	53 (44, 67)	0.78

*Defined as postprocedure minimal lumen diameter minus 6-month follow-up minimal lumen diameter. †Late loss divided by acute gain in minimal lumen diameter. ‡>50% stenosis after an initially successful procedure. §Actual percent stenosis. Data presented are median value (25th, 75th percentile) or percent of patient group.

50% of patients experiencing reocclusion within 6 months (1–4). Unfortunately, clinical trials evaluating the efficacy of ≥20 pharmacologic agents have failed to demonstrate any significant success in modifying the rate of restenosis after balloon angioplasty (5–12). In contrast, our observational study revealed that the use of estrogen replacement therapy was associated with an overall reduction in late loss in target vessel lumen after percutaneous coronary intervention in postmenopausal women. This beneficial effect of estrogen replacement therapy appears to be significantly greater in women undergoing directional coronary atherectomy than in those receiving conventional angioplasty.

Potential mechanism of action. Several potential mechanisms may account for the ability of estrogen to attenuate restenosis. Multiple observational studies and a recent randomized trial (30) demonstrated that estrogen alone and in combination with a progestin in postmenopausal women lowers serum low density lipoprotein and increases high density lipoprotein levels. We also noted that women receiving estrogen replacement therapy had significantly greater high density lipoprotein levels. This favorable modulation of lipoprotein metabolism therefore may provide a partial explanation for the lower angiographic measures of restenosis after percutaneous coronary intervention. However, available data on the effects of lovastatin (31), a more potent modifier of lipid profiles than estrogen, have failed to reveal any prevention of or reduction in restenosis. Likewise, significant differences between estrogen users and nonusers persisted after we adjusted for differences in high density lipoprotein levels. As a result, it seems improbable that the favorable lipoprotein effects of estrogen entirely account for the reduction in restenosis measures observed.

Estrogen has also been shown (16–19) to have direct effects on the vasomotion of normal and atherosclerotic arteries through endothelium-dependent and endothelium-independent mechanisms. Recent studies (20,21) have demonstrated that both short-term and long-term estrogen replacement therapy reverse the pathologic vasoconstriction observed in atherosclerotic vessels. These findings demonstrate that estrogen may promote vasodilation in diseased coronary arteries and potentially reduce pathologic vasoconstriction after percutaneous coronary intervention.

In addition, estrogen may prevent restenosis by altering cellular migration and neointimal proliferation after coronary intervention. After balloon-induced arterial injury, estrogen decreased platelet and neutrophil deposition at the site of injury (22). In vitro, physiologic levels of estrogen have been shown (23) to inhibit proliferation of vascular smooth muscle

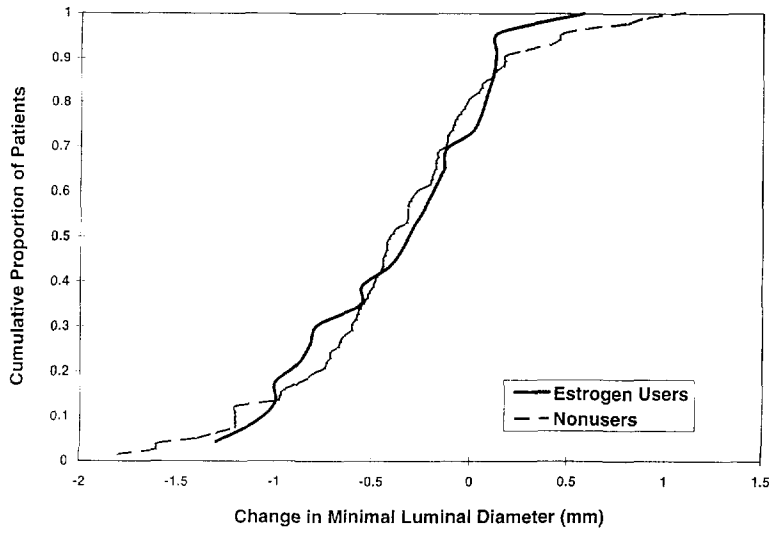

Figure 2. Cumulative frequency distribution of late loss in minimal lumen diameter of the target lesion in estrogen users and nonusers undergoing angioplasty.

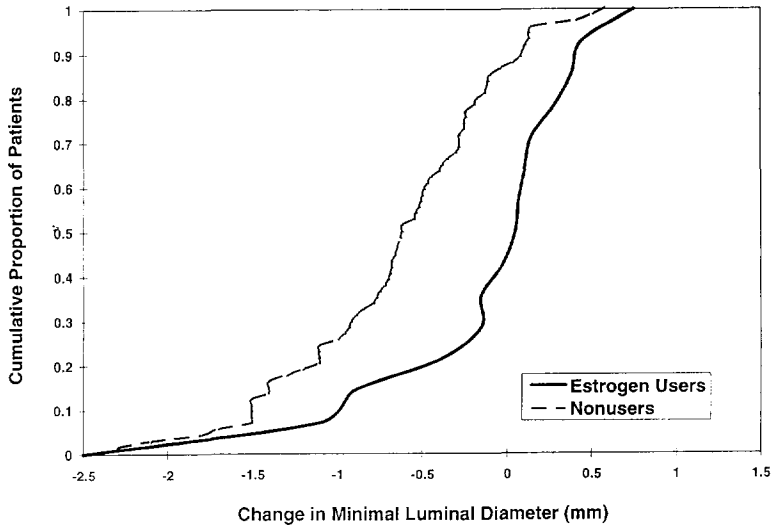

Figure 3. Cumulative frequency distribution of late loss in minimal lumen diameter of the target lesion in estrogen users and nonusers undergoing atherectomy.

from the coronary arteries of female pigs. Several studies have evaluated the ability of estrogen to alter vascular responses to injury in animal models. Although the results to date have been conflicting, the majority of studies (24–26) reported that estrogen significantly inhibited neointimal proliferation after arterial balloon injury. In contrast, a recent report by Geary and colleagues (27) concluded that estrogen did not inhibit balloon-induced proliferation of the intima in a nonhuman primate model.

Device-specific response. The present study was the first to clinically evaluate the effect of estrogen replacement therapy on restenosis in humans. We found an overall beneficial association between the use of estrogen replacement therapy and a reduction in late lumen loss after percutaneous coronary intervention. Although stratification by type of coronary intervention resulted in small subgroups (n = 97 and 107 for atherectomy and angioplasty, respectively), we found that estrogen replacement therapy was associated with a significant reduction in restenosis in patients who underwent atherectomy, whereas the effects were equivocal after conventional angioplasty. In fact, there was no significant loss in median lumen diameter among the 18 patients using estrogen who received atherectomy as compared with a 36% loss in minimal lumen diameter in those not receiving estrogen therapy. Among those who received balloon angioplasty, estrogen users and nonusers had similar late angiographic results (−0.29 vs. −0.39 mm late loss in minimal lumen diameter, p = 0.77).

Table 5. Clinical Outcomes at One-Year Follow-Up

	Estrogen Users (n = 47)	Estrogen Nonusers (n = 196)	p Value
Death	0	6 (3.0%)	0.24
Myocardial infarction	3 (6.4%)	14 (6.9%)	0.94
Coronary artery bypass surgery	3 (6.4%)	21 (10.3%)	0.44
Need for nonsurgical coronary intervention in the target artery	12 (25.5%)	58 (28.6%)	0.69
CCS class II, III or IV*	5 (10.6%)	31 (21.3%)	0.29
Composite clinical end point†	15 (31.9%)	71 (35.5%)	0.75

*Rates are based on proportion of patients with follow-up between 8 and 16 months after randomization. †The 1-year composite clinical end point was defined as death, myocardial infarction, coronary artery bypass surgery and nonsurgical coronary intervention in the target artery. Data presented are number of patients (rates by Kaplan-Meier survival analysis). CCS = Canadian Cardiovascular Society.

These findings suggest that the effect of estrogen replacement therapy may be device specific. Such a device-specific response is also consistent with our current understanding of the pathophysiology of restenosis after coronary intervention. Although both neointimal hyperplasia and late recoil have been implicated in restenosis, the former may have a significantly greater role in restenosis after atherectomy than after conventional balloon angioplasty (32–34). Because previous in vitro and animal studies (23–26) have indicated that the presence of estrogen can reduce neointimal proliferation, our results demonstrating a greater impact of estrogen on restenosis after atherectomy may support this mechanism of action. However, further evaluation is necessary as our study is the first to investigate arterial responses to estrogen after atherectomy injury.

Limitations. This analysis was exploratory and several limitations need to be emphasized. Most important, the results are based on retrospective and nonrandomized data. Patients using estrogen replacement therapy differed from those not using estrogen. Although many differences in baseline characteristics between estrogen users and nonusers failed to reach statistical significance, the cumulative effect may account for the variance in angiographic outcomes. Estrogen users undergoing atherectomy were also significantly younger and had a greater family history of coronary artery disease than did nonusers. However, known potential confounding factors for restenosis were adjusted for in our primary end point analyses. Even after adjusting for diabetes, unstable angina and lesion location in the left anterior descending artery, the use of

estrogen replacement therapy remained the most significant factor predicting late loss.

A second limitation was our limited overall sample size, particularly when we stratified the analyses by type of coronary intervention used. This limited sample size increases the possibility of a chance or spurious finding. However, our primary angiographic end point was prospectively defined and ascertained and the reviewer did not know the patient's estrogen status. Despite this, confirmation of these subgroup analyses in larger clinical data bases, when available, is indicated.

The study's limited sample size also constrained our ability to demonstrate potentially significant differences in clinical outcomes between estrogen users and nonusers. Although estrogen users had slightly fewer deaths and myocardial infarctions and demonstrated a trend toward a lower rate of exertional angina at 1-year follow-up, the study was not adequately powered to detect differences in clinical outcome. Recent preliminary evidence from Kim and colleagues (35) suggests that estrogen replacement therapy may improve long-term survival after percutaneous interventions in postmenopausal women.

Conclusions. This exploratory study suggests that estrogen replacement therapy in postmenopausal women may reduce restenosis after coronary intervention, particularly in patients receiving directional coronary atherectomy. Given the potential clinical importance of these findings, the use of estrogen replacement therapy as a means of preventing restenosis after coronary intervention deserves further evaluation.

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