Assessment of Estrogen Status as a Marker of Prognosis in Women With Symptoms of Suspected Coronary Artery Disease Presenting for Stress Testing

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Estrogen status (ES) has previously been shown to be a marker of angiographic outcome in women. In light of this finding, a reevaluation of ES as a marker of prognosis was undertaken. Two thousand one hundred forty-three women who underwent stress testing for symptoms of suspected coronary disease were studied. ES was defined according to menopausal, ovarian, and hormone replacement therapy status. The end points of interest were all-cause mortality, cardiac death, and nonfatal myocardial infarction. Survival analysis was performed using the Kaplan-Meier method and Cox regression analysis with censoring at revascularization. Compared with 1,362 ES-positive women, the 781 ES-negative women had a higher frequency of unfavorable end points (all-cause death: ES positive 31 [2.3%] vs ES negative 94 [12%], $p < 0.0001$, cardiac death: ES positive 11 [0.8%] vs ES negative 38 [4.9%], $p < 0.0001$, and nonfatal myocardial infarction: ES positive 11 [0.8%] vs ES negative 17 [2.2%], $p = 0.007$). The Kaplan-Meier curve analysis indicated that ES was a marker of cardiac risk ($p < 0.0001$) in all women, as well as in postmenopausal women. Multivariate Cox regression analysis revealed that ES was an independent marker of risk ($p < 0.001$) when considered with other standard risk factors. Using logistic regression and area under the curve analyses, ES had incremental value compared with standard risk factors. In conclusion, ES appears to be an easily discernible independent marker of risk that provides incremental prognostic information compared with standard clinical variables in women with symptoms of suspected coronary disease presenting for stress testing. **© 2006 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2006;97:367–371)**

When evaluating patients with suspected coronary disease, men and women should be given equal consideration. However, despite equal consideration, significant differences still exist between men and women that make the evaluation somewhat less than equivalent.[1] One area of difference resides in the sexual hormone realm. Previous reports have indicated that defining a woman's hormonal status using a clinical marker called estrogen status (ES) can potentially reduce the diagnosis gap that exists between men and women concerning certain diagnostic test results.[2] Using angiographic data, women who were ES positive (i.e., not estrogen deficient) had a much lower prevalence of angiographic coronary disease than women who were ES negative (i.e., estrogen deficient). ES-positive women included those who were premenopausal, as well as those on hormone replacement therapy. Follow-up assessment of this relation between ES and coronary disease presence demonstrated that the relation was consistent across differing subgroups of the ES-positive group, including those receiving hormone replacement therapy.[3,4] ES as a diagnostic tool has found its way into several multivariate scores used to assess women with suspected coronary disease.[5,6] The purpose of the present study was to assess the ability of ES to stratify women with suspected coronary disease according to prognostic, rather than angiographic, outcomes.

Methods

Patient populations: All ambulatory women ≥18 years of age referred by primary care physicians and cardiologists to the stress laboratory were screened for their first stress test, which included exercise electrocardiographic, exercise and pharmacologic nuclear, or echocardiographic studies. Only symptomatic women referred for the express purpose of evaluating the presence of coronary disease were included. Asymptomatic women and those with a history of myocardial infarction or coronary angiography were excluded.

Baseline clinical information: The following data were collected from patients during a prestress test interview: age, symptoms, medication use at the time of the stress test, and other coronary risk factors. Patients also had their height and weight recorded. Chest pain was evaluated using

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the 3 categories of Diamond[7]: typical angina, atypical angina, and nonanginal chest pain. Risk factors included the following: current or previous cigarette smoking, history of hypertension (on antihypertensive therapy), history of insulin or non–insulin-dependent diabetes, history of high cholesterol or on cholesterol-lowering therapy, family history of premature (<60 years of age) coronary disease (infarction, coronary bypass or angioplasty, sudden death) in first-degree relatives, and obesity (defined as a body mass index >30 kg/m^2). The metabolic syndrome was diagnosed when 3 of the following 4 factors were present: obesity, hyperlipidemia, diabetes, or hypertension.

ES was determined using previously published criteria.[2] Women were ES negative if they were postmenopausal and not on estrogen replacement therapy. If they were premenopausal or receiving estrogen replacement therapy, they were considered ES positive. Women who underwent hysterectomy without oophorectomy were considered ES positive if they were <50 years old and without symptoms of estrogen deficiency. Otherwise, they were considered ES negative. Additional data were collected pertaining to the type of hormone replacement therapy and the interval from the cessation of menstrual periods.

Hormone replacement therapy was any of a variety of estrogenic compounds with or without a progestational agent. Estrogenic compounds included conjugated estrogen, estradiol (pill or patch), estropipate, estrogen plus testosterone, or generic estrogen (patient unsure of name of medication). Estrogen receptor modulators such a raloxifene were considered estrogenic compounds. Birth control pills or progestational agents alone were not considered hormone replacement therapy.

End point assessment: Patients had vital status and date of death determined by a search of the Social Security Death Index. The cause of death was supplied as *International Classification of Diseases,* 9th or 10 edition, codes by the West Virginia Department of Health and Human Resources. The cause of death could not be determined in 13 of the 254 deaths (5%). These patients were categorized as having noncardiac deaths. In addition, all medical records were reviewed concerning the first nonfatal acute myocardial infarction occurring after the stress test and the first percutaneous coronary intervention or coronary artery bypass surgery occurring after the stress test. Myocardial infarction was documented by history, cardiac enzyme elevations, and/or new Q waves on the electrocardiogram. The institutional human subjects committee approved the collection of all data.

Statistical analysis: The Number Cruncher Statistical System (NCSS 2004 software, www.ncss.com) was used for all statistical analyses. Comparison of frequencies was performed using chi-square testing. Comparison of means was performed using nonpaired *t* testing. Survival analysis was performed using Kaplan-Meier curves and Cox regression analysis with censoring for revascularization on the date of the first occurrence after stress testing. If the Kaplan-Meier method revealed a significant relation between the end point and predictor variable, Cox multivariate analysis was used to determine whether the relation was independent of other important clinical predictors. Smoking, diabetes, hypertension, hyperlipidemia, family history of coronary disease, and obesity, as defined earlier, were added to the ES variable into a Cox model. All these variables were dichotomous variables (i.e., 1 = present or ES positive and 0 = absent or ES negative). In addition, either age (all women) or years since menopause (postmenopausal women) was included as a continuous variable. Those ES-positive women aged <50 with hysterectomy but intact ovaries were excluded from the postmenopausal group. This was performed to limit the ES-positive postmenopausal women to those receiving hormone replacement therapy. The incremental value of ES compared with the other clinical data was assessed by comparing the area under receiver-operating characteristic (ROC) curves. Logistic regression analysis was used to generate probabilities to determine the area under the curve. The variables considered in the logistic regression model were ES, smoking, diabetes, hypertension, hyperlipidemia, family history of coronary disease, obesity, and either age or years since menopause, as with the Cox analysis. The present or absence of an event was the dependent variable. p Values <0.05 were considered significant.

Table 1
Clinical characteristics and outcomes

Variable	ES Positive (n = 1,362)	p Value	ES Negative (n = 781)
Age (yrs)	47 ± 11	<0.00001	63 ± 11
Anginal symptoms			
Typical	119 (9%)		70 (9%)
Atypical	587 (43%)	0.97	333 (43%)
Nonanginal	656 (48%)		378 (48%)
Diabetes mellitus	188 (14%)	<0.00001	174 (22%)
Smoker	541 (40%)	0.33	327 (42%)
Hyperlipidemia	429 (31%)	<0.00001	322 (42%)
Hypertension	524 (39%)	<0.00001	411 (53%)
Obesity (body mass index >30 kg/m^2)	686 (50%)	0.15	368 (47%)
Metabolic syndrome	210 (15%)	<0.00001	185 (24%)
Normal electrocardiogram at rest	1,111 (82%)	<0.00001	540 (69%)
Pharmacologic stress	286 (21%)	<0.00001	362 (46%)
All-cause death	31 (2.3%)	<0.00001	94 (12%)
Cardiac death	11 (0.8%)	<0.00001	38 (4.9%)
Nonfatal myocardial infarction	11 (0.8%)	0.007	17 (2.2%)
Cardiac death/myocardial infarction	22 (1.6%)	<0.00001	55 (7.0%)

Results

Patient populations: From 1995 to 2001, 2,143 symptomatic women with suspected coronary disease underwent

Table 2
Cardiac outcomes according to estrogen status and subgroups

	All Women			No Revascularization		
	Total	ACM	CDMI	Total	ACM	CDMI
ES positive	1,362	31 (2.3%)	22 (1.6%)	1,335	27 (2.0%)	19 (1.4%)
Premenopausal	639	8 (1.3%)	6 (1.0%)	630	7 (1.2%)	6 (1.0%)
Hysterectomy, intact ovaries, age ≤50 yrs	97	3 (3.1%)	2 (2.1%)	95	2 (2.1%)	1 (1.1%)
HRT, nonsurgical menopause	178	6 (3.4%)	2 (1.1%)	176	6 (3.4%)	2 (1.1%)
HRT, hysterectomy, ovaries in	155	4 (2.6%)	5 (3.2%)	147	2 (1.4%)	3 (2.0%)
HRT, hysterectomy, ovaries out	293	10 (3.4%)	7 (2.4%)	287	10 (3.5%)	7 (2.4%)
ES negative	781	94 (12.0%)	55 (7.0%)	764	91 (11.9%)	53 (7.1%)
Nonsurgical menopause	480	64 (13.3%)	39 (8.1%)	475	62 (13.1%)	38 (7.9%)
Hysterectomy, intact ovaries, age >50 yrs	90	8 (8.9%)	4 (4.4%)	88	8 (9.1%)	4 (4.5%)
Hysterectomy, ovaries out	208	22 (10.6%)	12 (5.8%)	198	21 (10.6%)	11 (5.6%)

ACM = all-cause mortality; CDMI = cardiac death or nonfatal myocardial infarction; HRT = hormone replacement therapy.

stress testing (Table 1). Compared with ES-negative women, ES-positive women were younger and had a lower frequency of diabetes, hyperlipidemia, hypertension, positive family history of premature coronary disease, metabolic syndrome, abnormal electrocardiographic findings at rest, and pharmacologic stress referral. The 2 groups had similar symptom presentations. The overall annualized all-cause death rate was 1.3%, which would make this a low-to-intermediate risk cohort. ES defined ES-negative or high-risk (2.7% annualized all-cause death) and ES-positive or low-risk (0.5% annualized all-cause death) subgroups with significant differences for all end points assessed. A total of 626 women were receiving hormone replacement therapy at the time of the stress test: conjugated estrogen in 318 (plus progestin in 137), estradiol pill in 61 (plus progestin in 12), estradiol patch in 30 (plus progestin in 3), estropipate in 7 (plus progestin in 1), estrogen plus testosterone in 12 (plus progestin in 1), generic estrogen in 27 (plus progestin in 5), and raloxifene in 12.

Estrogen status and risk: Table 2 lists the outcome results according to ES, as well as the several subgroups within each classification with and without consideration of coronary revascularization after the stress evaluation. The data in Table 2 indicate that the risk within subgroups of ES is internally consistent with the overall risk of the ES-positive and ES-negative groups. Thus, those defined as ES positive had a low risk compared with those defined as ES negative.

Figures 1 and 2 display the Kaplan-Meier curves for all women and postmenopausal women, respectively. These curves revealed a highly significant difference between ES-positive and ES-negative women concerning the time to cardiac death or nonfatal myocardial infarction. Table 3 lists the results of the multivariate Cox analysis. Only variables that were significant predictors ($p < 0.05$) were included. For all women and postmenopausal women, as defined earlier, ES was an independent predictor of risk. This was especially true for the postmenopausal women for whom

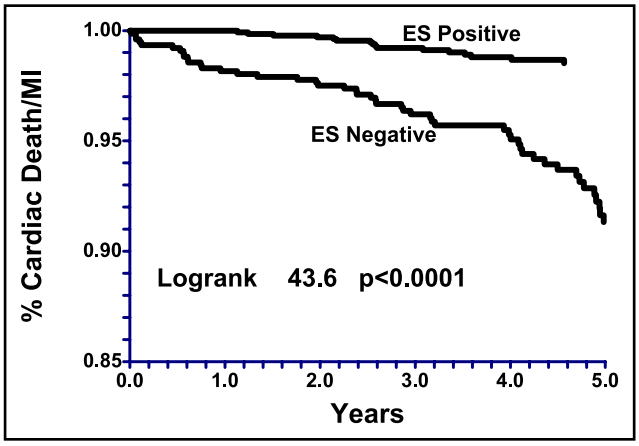

Figure 1. Kaplan-Meier curves for ES-positive and ES-negative subgroups within all women not undergoing revascularization. Outcome was cardiac death or nonfatal myocardial infarction (MI). See text for discussion.

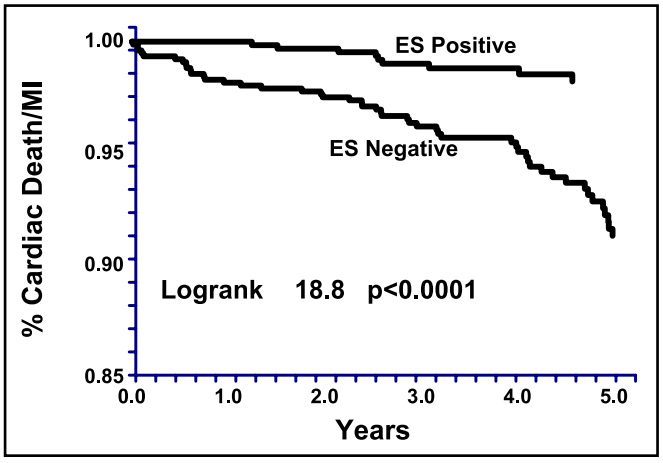

Figure 2. Kaplan-Meier curves for ES-positive and ES-negative subgroups within all postmenopausal women not undergoing revascularization. Outcome was cardiac death or nonfatal myocardial infarction (MI). See text for discussion.

Table 3
Cox analysis results

	All-cause Death			Cardiac Death/Nonfatal Myocardial Infarction		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
All women						
ES	0.47	0.28–0.77	0.003	0.52	0.28–0.96	0.03
Age	1.06	1.04–1.08	<0.0001	1.05	1.02–1.07	<0.0001
Hypertension	1.49	1.00–2.19	0.04	2.01	1.20–3.37	0.007
Diabetes	2.61	1.77–3.86	<0.0001	1.81	1.06–3.07	0.02
Smoking	1.91	1.31–2.78	0.0007	1.62	1.00–2.61	0.04
Postmenopausal women						
ES	0.29	0.17–0.48	<0.0001	0.35	0.18–0.66	0.001
Years since menopause	1.01	0.99–1.03	0.06	1.02	1.00–1.04	0.04
Hypertension	1.76	1.17–2.63	0.006	2.10	1.24–3.58	0.006
Diabetes	2.69	1.79–4.02	<0.0001	1.90	1.10–3.28	0.02

CI = confidence interval.

estrogen positivity meant the presence of hormone replacement therapy.

The areas under the ROC curves were compared with and without ES in women who did not undergo revascularization. For all-cause death in all women, the model ROC curve area improved from 0.84 ± 0.02 to 0.85 ± 0.02 ($p = 0.03$). However, for postmenopausal women only, the model ROC curve area improved from 0.78 ± 0.02 to 0.83 ± 0.02 ($p < 0.001$). For cardiac death/myocardial infarction in all women, the model ROC curve area tended toward improvement from 0.81 ± 0.02 to 0.82 ± 0.02 ($p = 0.09$). However, for only postmenopausal women, the model ROC curve area improved from 0.75 ± 0.03 to 0.78 ± 0.03 ($p < 0.05$).

A total of 614 women who were on hormone replacement therapy did not undergo revascularization. Of these 614 women, 453 (74%) were receiving estrogen alone at the time of the stress test. The remainder were receiving a combination of estrogen and progestin. The outcomes for these 2 groups were compared. The all-cause death rate for those taking estrogen alone was 2.9% (13 of 453) and was 3.1% (5 of 161) for those taking estrogen plus progestin ($p = 0.88$). The cardiac death/myocardial infarction rate for those taking estrogen alone was 2.4% (11 of 453) and was 0.6% (1 of 161) for those taking estrogen plus progestin ($p = 0.15$).

Discussion

The results of the present study have suggested that ES is a marker of cardiac risk in women with symptoms of suspected coronary disease. This marker is independent of other established risk factors. In addition, its ability to predict risk is consistent within a number of defined subgroups of each of the 2 ES designations. Its incremental value was modest, but its value was higher in postmenopausal women. This emphasizes the point that its proper clinical role is in the multivariate scores mentioned earlier,[5,6] and not as a standalone variable.

However, if the randomized trials conducted thus far have correctly defined the truth concerning estrogen replacement therapy and cardiovascular risk, how can our ES results be explained? Numerous previous observational studies have demonstrated that, even after adjustment for other clinical data, women who take estrogen replacement therapy have better clinical outcomes than women who do not.[8] However, such studies are problematic, given that important variables such as socioeconomic and insurance status, as well as medication compliance and tolerance, were often not available for inclusion in the analyses. ES could be a surrogate for some other covariate, such as a healthy lifestyle or health awareness. Just such a hypothesis has been suggested by Husak et al.[4]

These results cannot be applied to patients with known coronary disease or those without symptoms suggestive of coronary disease. In addition, the results reflect ES at the time of the stress test and do not consider changing ES, such as starting or discontinuing estrogen replacement after the stress test. Our analysis simulated more of an "intention to treat" rather than a "crossover" analysis. There were 13 patients for whom the cause of death could not be determined. In the foregoing analysis, these patients were categorized as having noncardiac deaths. However, when the analysis was conducted by classifying them as cardiac deaths, no significant change was found in the results. Because we used a hospital-based medical record to assess for the nonfatal end points of myocardial infarction and revascularization, it is possible that some of those end points were missed in those patients who had those end points at other institutions. Nevertheless, these conclusions could be based solely on all-cause or cardiac death, end points that are more robust in this respect.

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