

Risk Factors and Secondary Prevention in Women with Heart Disease: The Heart and Estrogen/progestin Replacement Study

Eric Vittinghoff, PhD; Michael G. Shlipak, MD, MPH; Paul D. Varosy, MD; Curt D. Furberg, MD, PhD; Christine C. Ireland, MPH; Steven S. Khan, MD; Roger Blumenthal, MD; Elizabeth Barrett-Connor, MD; and Stephen Hulley, MD, MPH, for the Heart and Estrogen/progestin Replacement Study Research Group

Background: Risk factors for coronary heart disease events have most commonly been evaluated in healthy men.

Objective: To assess risk factors, event rates, and use of secondary prevention treatments in women with preexisting coronary disease.

Design: A prospective cohort of clinical trial participants.

Setting: 20 U.S. clinical centers.

Participants: 2763 postmenopausal women with known coronary disease in the Heart and Estrogen/progestin Replacement Study (HERS).

Measurements: Myocardial infarction or death from coronary heart disease.

Results: On multivariable analysis, the researchers found 11 risk factors: 6 noted by history (nonwhite ethnicity, lack of exercise, treated diabetes, angina, congestive heart failure, and more than one previous myocardial infarction) and 5 that were measured (blood pressure, low-density lipoprotein cholesterol level, high-

density lipoprotein cholesterol level, lipoprotein(a) level, and creatinine clearance). The annual rate of coronary events was 1.3% (95% CI, 0.7% to 2.5%) in women with no risk factors and 8.7% (CI, 7.1% to 10.8%) in women with five or more risk factors (a sixfold increase). At entry into HERS, 83% of participants were receiving aspirin or other antiplatelet agents, 33% were receiving β -blockers, 18% were receiving angiotensin-converting enzyme inhibitors, and 53% were receiving lipid-lowering drugs. Women with more risk factors were less likely to be taking aspirin ($P < 0.001$) and lipid-lowering drugs ($P = 0.006$).

Conclusions: Women with coronary disease are at high risk for myocardial infarction or death from coronary heart disease even in the absence of other risk factors, and their risk increases up to sixfold when many risk factors are present. Established drugs for secondary prevention, including aspirin, β -blockers, and lipid-lowering agents, are underused in these women, especially those at highest risk.

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For author affiliations, see end of text.

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Coronary heart disease (CHD) is the leading cause of death in women. The major independent risk factors that predict CHD onset in healthy women are similar to those identified by epidemiologic studies of healthy men (1-7). A recent report described six independent risk factors—age, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, high blood pressure, diabetes mellitus, and smoking—that were strongly associated with risk for a first CHD event in both men and women (8). However, the strength of the association of certain risk factors with CHD events may vary by sex (9) as well as age. Diabetes may be a stronger risk factor in women than in men (7); among older women, HDL cholesterol level may be a relatively strong risk factor and LDL cholesterol level a relatively weak one (6).

In the period immediately after myocardial infarction (MI), studies of mostly male samples have found that persistent ischemia, impaired left ventricular systolic function, and ventricular arrhythmias are the major determinants of subsequent MI and death (10-13). In the Coronary Drug Project study of men with a history of heart attack, electrocardiographic abnormalities and heart failure were stronger predictors than the atherosclerosis risk factors identified in primary prevention settings (14). However, the risk factors for coronary events among women with recognized but stable coronary disease are mostly unknown. Better understanding of these factors could im-

prove secondary prevention in this large and high-risk group.

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized clinical trial of estrogen plus progestin for prevention of CHD events in women with coronary disease (15). Overall, no significant differences were noted between the hormone and placebo groups in CHD events; trends of more CHD events with therapy in year 1 were offset by fewer such outcomes during years 4 and 5. The trial collected extensive data on CHD risk factors and medication use and performed exhaustive outcome ascertainment procedures, with complete mortality follow-up. Therefore, HERS offers a unique opportunity to assess the long-term effect of coronary risk factors and use of recommended treatments in women with established coronary disease.

METHODS

Participants

Participants in HERS were postmenopausal women who were younger than 80 years of age, had not had a hysterectomy, and had known coronary artery disease (MI, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or angiographic evidence of $\geq 50\%$ narrowing of one or more major coronary arteries). Women were excluded if they had had a coronary event

Context

Risk factors for recurrent events among women with known coronary disease and whether these women commonly receive secondary prevention treatments are mostly unknown.

Contribution

This large cohort study showed that 11 different factors, including several previous infarctions, renal dysfunction, diabetes, angina, heart failure, and uncontrolled hypertension, predicted up to a sixfold increased rate of coronary disease events in postmenopausal women with preexisting coronary disease. Despite high risks, half or fewer women were taking β -blockers, angiotensin-converting enzyme inhibitors, or cholesterol-lowering drugs.

Implications

Clinicians can identify women who have high risks for recurrent coronary events and should promote greater use of secondary prevention treatments for them.

—The Editors

within the 6 months before randomization, had a serum triglyceride level greater than 3.39 mmol/L (300 mg/dL), had used hormones within 3 months, or had a history of conditions that would contraindicate estrogen therapy (16). Participants in HERS were randomly assigned within clinical centers to 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate in one tablet daily ($n = 1380$) or a placebo of identical appearance ($n = 1383$). The institutional review boards at the coordinating center and each of the 20 HERS clinical centers approved the protocol, and all participants provided written informed consent.

Predictors

In the baseline interview, information was obtained by self-report on demographic characteristics, behavioral risk factors, and medical history. Among women who reported ever having smoked at least 100 cigarettes, years of smoking, average cigarettes per day, and current smoking were ascertained. Alcohol use in the past 30 days was assessed for frequency and usual numbers of drinks per occasion. Exercise was measured as participation in a “regular exercise program such as cardiac rehabilitation or aerobics” or walking at least occasionally “for exercise more than 10 minutes at a time.” Use of aspirin, β -blockers, lipid-lowering medications (statins, niacin, fibrates, bile acid-binding resins, and probucol), angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and folate or vitamin B was assessed by self-report.

In the baseline physical examination, blood pressure, waist-to-hip ratio, and body mass index were measured. A physician assessed history and symptoms of heart failure (jugular venous distension, third heart sound, significant

murmurs, pulmonary rales, and peripheral edema). High blood pressure was defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg, according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (17). Angina was defined as self-report of chest discomfort in the previous 4 weeks during exercise, emotion, or sexual activity. Serum specimens were obtained, and a centralized laboratory measured fasting levels of LDL cholesterol, HDL cholesterol, lipoprotein(a), triglycerides, glucose, and creatinine (15, 16). Creatinine clearance was estimated by using the Cockcroft–Gault equation (18, 19).

Outcomes

The primary HERS outcome was CHD events, defined as nonfatal MI or CHD death. Suspected outcome events were reported within 24 hours to the coordinating center and were systematically assessed every 4 months at the follow-up contacts. An independent morbidity and mortality subcommittee that was blinded to treatment assignment adjudicated all deaths and suspected outcome events. Nonfatal MI was diagnosed by using an algorithm based on ischemic symptoms, electrocardiographic abnormalities, and elevated cardiac enzyme levels (16). Death from CHD included fatal documented MI, sudden death within 1 hour of symptom onset, unobserved death that occurred out of the hospital in the absence of other known causes, or death due to a coronary revascularization procedure or congestive heart failure. The date of each event was determined from the documentation obtained by the clinical centers. The total number of events reported here is slightly larger than that published in the primary HERS results (15) because of subsequent adjudications (20).

Statistical Analyses

We used multivariable Cox proportional hazards models to assess the associations between risk factors and CHD events. These models were stratified by clinical center to account for potential clustering. Waist-to-hip ratio and LDL and HDL cholesterol levels were modeled as continuous variables, but lipoprotein(a) level was dichotomized at the median and creatinine clearance was dichotomized at 0.66 mL/s (40 mL/min) to reflect the nonlinear responses we have reported elsewhere (19, 21). We used an indicator for any alcohol use, since almost all of the 39% of HERS women who reported alcohol use were light or moderate drinkers. Exercise was modeled by an indicator for participation in an exercise program or walking for exercise for more than 10 minutes.

The multivariable model includes previously identified risk factors that were significant ($P \leq 0.20$) in unadjusted models and were not judged redundant on substantive grounds. Body mass index was excluded because it was clearly nonsignificant after adjustment ($P > 0.2$) and was also highly correlated with waist-to-hip ratio, which was

the stronger predictor in unadjusted analysis. Similarly, triglyceride levels were excluded because of their strong negative correlation with HDL cholesterol levels, which in our judgment were more likely to be causal. We also controlled for use of aspirin, statins, other lipid-lowering medications, diuretics, β -blockers, ACE inhibitors, calcium antagonists, and folate or vitamin B. The effect of assignment to hormone therapy was modeled separately for each year of follow-up, as in the post hoc analysis of HERS (15).

Interactions between risk factors and relevant treatments were also examined. Specifically, we compared hazard rates among patients with diagnosed diabetes who reported use of insulin or oral hypoglycemic agents with rates in the combined group of diabetic persons not using these medications and women with fasting glucose levels greater than 6.94 mmol/L (>125 mg/dL) but no history of diabetes diagnosis. Likewise, we compared estimates for LDL and HDL cholesterol levels stratified by use of any lipid-lowering medication or assignment to hormone therapy; for lipoprotein(a) level, stratified by assignment to hormone therapy; for high blood pressure on examination, stratified by use of at least one antihypertensive medication; for heart failure and creatinine clearance less than or equal to 0.66 mL/s (≤ 40 mL/min), stratified by use of ACE inhibitors; and for more than one previous MI and angina, stratified by use of any indicated medications. The final model includes interactions that were significant at a P value less than or equal to 0.2.

We used residuals to assess overall model fit, validity of the proportional hazards assumption, and linearity of associations with continuous predictors. The study lacked power to examine interactions between clinical center and potential risk factors. We tested the assumption of non-informative censoring by considering the two extremes of the possible outcomes for the 60 women lost to clinical follow-up before the end of HERS, first as events at the time of censoring, then as observations censored at the longest observed follow-up time.

The average annual rate of CHD events was estimated overall and for groups defined by number of risk factors present among the 11 predictors identified in the multivariable Cox model. To evaluate this number, LDL and HDL cholesterol levels were dichotomized at standard cut-points for elevated risk. Within these groups, we tabulated use of aspirin and other antiplatelet agents, β -blockers, ACE inhibitors, and lipid-lowering therapy, both at baseline and at the end of the study. We also tabulated the proportions of women with various risk factors who were receiving indicated treatments. Because the third report of the National Cholesterol Education Program has only recently been published (22), the denominator for lipid-lowering medication use excluded nonusers with LDL cholesterol levels less than 3.4 mmol/L (<130 mg/dL), which was the criterion for initiating therapy among women with coronary disease in the second report of the National Cholesterol Education Program (NCEP II) (23). Similarly, the

denominator for use of aspirin or other antiplatelet agents excluded women using warfarin. All analyses were performed by using SAS, version 8.02 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

Wyeth-Ayerst Research funded the HERS clinical trial, implemented data collection, and reviewed the manuscript before submission for publication. The investigators were not required by contract to make any revisions suggested by Wyeth-Ayerst.

RESULTS

During an average of 4.1 years of follow-up in 1993 to 1998, 361 of 2763 women in HERS had nonfatal MI or died of CHD. Of the 232 women with nonfatal MI, 24 subsequently died of CHD. The 129 CHD deaths included 35 fatal MIs, 38 sudden deaths, 16 deaths from congestive heart failure or pulmonary edema, 24 deaths that were unwitnessed or occurred during sleep, and 16 deaths from other or unclassified CHD causes.

Unadjusted Analyses

Nonwhite women were twice as likely as white women to have a CHD event (Table 1). Both alcohol use and regular exercise were associated with lower event rates. Treated diabetes, congestive heart failure, a history of at least two MIs, and angina by self-report were associated with increased event rates. Higher blood pressure, waist-to-hip ratio, LDL cholesterol level, and triglyceride levels, as well as lower HDL cholesterol level and creatinine clearance (≤ 0.66 mL/s [≤ 40 mL/min]) were associated with CHD events.

Adjusted Analyses

In the multivariable model (Table 2), increased rates of CHD events were associated with diabetes (among those taking insulin or oral hypoglycemic agents), high blood pressure, at least two previous MIs, heart failure, angina, creatinine clearance less than or equal to 0.66 mL/s (≤ 40 mL/min), lipoprotein(a) level at least 0.90 mmol/L (≥ 25.3 mg/dL) among women assigned to placebo, lack of exercise, and African-American ethnicity. We also found probable associations with higher LDL and lower HDL cholesterol levels ($P = 0.06$ for both). Weaker evidence was observed for increased rates among Latin-American women and women of other nonwhite ethnicity, older women, and current smokers. The findings were similar if weak predictors (including former smoking, untreated diabetes, lipoprotein(a) level among women assigned to hormone therapy, and previous percutaneous transluminal coronary angioplasty) were excluded from the model, or if we used a quantitative measure of alcohol use. The estimate for HDL cholesterol level was attenuated if triglyceride level was added to the model shown in Table 2, but triglyceride level is the weaker predictor and was nonsignificant. Furthermore, triglyceride level was not statistically significant in a

Table 1. Risk Factors for Coronary Heart Disease Events*

Risk Factor	Participants without CHD Events (n = 2402)	Participants with CHD Events (n = 361)	Relative Hazard (95% CI)†	P Value
Demographic characteristics				
Mean age at randomization ± SD, y	66.6 ± 6.6	66.9 ± 6.7	1.11 (0.95–1.30)	0.2
Ethnicity, %				
African American	7	14	2.05 (1.52–2.77)	<0.001
Latin American	2	3	1.61 (0.86–3.03)	0.14
Other nonwhite	1	2	1.87 (0.93–3.78)	0.08
Health-related behaviors, %				
Smoking				
Current	13	15	1.24 (0.93–1.65)	0.14
Former	50	44	0.84 (0.67–1.06)	0.14
Any alcohol consumption	40	31	0.67 (0.53–0.83)	<0.001
Exercise‡	66	53	0.60 (0.49–0.74)	<0.001
Medical conditions, %§				
Diabetes				
Receiving insulin or oral hypoglycemic agents	17	29	2.01 (1.59–2.54)	<0.001
Other	8	8	1.12 (0.76–1.66)	>0.2
≥2 previous myocardial infarctions	5	9	1.88 (1.30–2.72)	<0.001
Previous PTCA	44	40	0.85 (0.69–1.05)	0.14
Angina	25	36	1.66 (1.34–2.05)	<0.001
Physical examination				
Mean BMI ± SD, kg/m ²	28.5 ± 5.4	29.1 ± 6.1	1.09 (0.98–1.20)	0.10
Mean waist-to-hip ratio ± SD	0.87 ± 0.08	0.88 ± 0.08	1.15 (1.04–1.28)	0.007
High blood pressure, %	37	49	1.61 (1.31–1.98)	<0.001
History or symptoms of CHF, %	11	19	1.76 (1.35–2.28)	<0.001
Laboratory results				
Mean LDL cholesterol level ± SD, mmol/L (mg/dL)	3.74 ± 0.97 (144 ± 38)	3.90 ± 1.02 (151 ± 40)	1.15 (1.05–1.27)	0.004
Mean HDL cholesterol level ± SD, mmol/L (mg/dL)	1.31 ± 0.34 (50.6 ± 13.3)	1.25 ± 0.32 (48.3 ± 12.4)	0.85 (0.76–0.95)	0.004
Lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL), %				
Placebo group	24	30	1.49 (1.11–2.00)	0.008
Hormone therapy group	25	25	0.97 (0.72–1.30)	>0.2
Mean triglyceride level ± SD, mmol/L (mg/dL)	1.87 ± 0.71 (165 ± 63)	1.96 ± 0.75 (173 ± 66)	1.14 (1.03–1.26)	0.01
Creatinine clearance ≤ 0.66 mL/s (≤40 mL/min), %	11	17	1.78 (1.35–2.34)	<0.001

* Coronary heart disease events include nonfatal myocardial infarction and death from CHD. All listed risk factors were previously identified as associated with CHD events in unadjusted analysis ($P \leq 0.20$). Additional variables screened in preliminary analysis include education, marital status, living situation, heart rate, and individual signs of heart failure. BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTCA = percutaneous transluminal coronary angioplasty.

† From unadjusted Cox models. The relative hazard is per 10 years for age and per SD for BMI; waist-to-hip ratio; and LDL cholesterol, HDL cholesterol, and triglyceride levels.

‡ Defined as regular participation in an exercise program or walking for at least 10 minutes.

§ Other women with diabetes include those reporting a history of diagnosis but no medication use and women with fasting plasma glucose levels > 6.94 mmol/L (>125 mg/dL). Angina was defined by self-report as chest pain in the past 4 weeks during exercise, emotion, or sexual activity.

|| High blood pressure is defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

multivariable model from which HDL level was excluded. The multivariable model was determined by using data for 2740 of 2763 women (99%) with no missing covariate values and included 354 of the 361 observed events (98%). We found little evidence for violation of the proportional hazards assumption ($P > 0.2$). However, the results for HDL cholesterol level and smoking were uncertain because they were sensitive to the untestable assumption of non-informative censoring.

CHD Events and Use of Medications by Number of Risk Factors

Overall, the average annual rate of CHD events was 3.4% (95% CI, 3.1% to 3.8%) (Table 3). Half of all women had at least two risk factors. Average annual rates increased sixfold, from 1.3% among women with no risk factors to 8.7% among women with five or more risk factors ($P < 0.001$ for trend). Despite this increasing gradient, women with five or more risk factors appeared to be

the least likely to receive aspirin ($P < 0.001$ for trend) and lipid-lowering therapy ($P = 0.006$ for trend). Use of β -blockers was similar across subgroups. Use of ACE inhibitors, however, increased with the number of risk factors ($P < 0.001$ for trend).

Time Trends in Secondary Prevention

We also examined use of these secondary prevention drugs at the end of the study. Use of aspirin and other antiplatelet agents had decreased slightly from 83% to 79%, and use of β -blockers was essentially unchanged (33% vs. 35%) (Table 3). Use of any lipid-lowering medication had increased from 53% to 66% among women who met NCEP II criteria; most were taking statins. The associations at baseline between number of risk factors and use of aspirin or other antiplatelet agents, ACE inhibitors, and lipid-lowering therapy persisted at the end of the study.

Use of Indicated Medications by Risk Factor

For certain risk factors, we evaluated the proportions of women using indicated medications. Only 37% of women with diagnosed heart failure and only 24% of women with creatinine clearance of 0.66 mL/s or less (≤ 40 mL/min) used ACE inhibitors (Table 4). Use of β -blockers and aspirin or other antiplatelet agents was similar among women with previous MI and those with angina symptoms.

DISCUSSION

We found 11 risk factors for MI or coronary death in our cohort of women with previous coronary artery disease. Of these factors, 6 were noted by history (nonwhite ethnicity, lack of exercise, treated diabetes, angina, congestive heart failure, and more than one previous MI) and 5 were measured (blood pressure, LDL cholesterol level, HDL cholesterol level, lipoprotein(a) level, and creatinine clearance). Compared with women in primary prevention settings (8), women with no risk factors had a substantial absolute risk for nonfatal MI or CHD death. This risk was increased sixfold in women with five or more risk factors.

Two of the six conventional risk factors that were independent predictors of CHD events in healthy middle-aged women in the Framingham Study (8) were not risk factors in HERS. The nonsignificant relative hazard estimates for age and smoking in our study appear to differ from findings in other samples of persons with coronary disease (14, 24), but wide confidence intervals suggest that the differences between studies would not be statistically significant. In addition, because smoking was not prevalent in HERS, we had less power to detect a clinically relevant association. The relative hazards for diabetes, high blood pressure, LDL cholesterol level, and HDL cholesterol level in women in HERS, while statistically significant, were somewhat weaker than those estimated in women without CHD (6, 8) and resemble findings in men with previous coronary disease (14). The excess event rates associated with these risk factors are greater than in primary prevention because the baseline rate in the secondary prevention setting is substantially higher (25).

Differing patterns of risk factors in HERS compared with primary prevention settings may result from differences in age or in the presence of established coronary disease. Participants in HERS were on average 67 years of age, and some risk factors, notably serum cholesterol level and tobacco use, may become less predictive of CHD events as age increases (26, 27). In addition, determinants of atherosclerosis, which play a central role in predicting CHD risk in patients without manifest coronary disease, may be less important than measures of recurrent ischemia, myocardial function, and arrhythmia in patients in whom coronary disease has been established (10–13, 28).

Although all participants in HERS had established coronary artery disease, only about half had had an MI

Table 2. Multivariate Cox Regression Analyses of Risk Factors for Coronary Heart Disease Events*

Risk Factor	Relative Hazard (95% CI)	P Value
Well supported by overall evidence, including previous findings		
Ethnicity		
African American	1.44 (1.02–2.04)	0.04
Latin American	1.92 (0.95–3.91)	0.07
Other nonwhite	1.87 (0.89–3.91)	0.10
Exercise program or walking for ≥ 10 minutes	0.80 (0.64–1.00)	0.05
High blood pressure on examination†	1.55 (1.16–2.07)	0.003
Diabetes treated with insulin or oral hypoglycemic agents‡	1.51 (1.16–1.98)	0.001
LDL cholesterol level (per SD)	1.10 (1.00–1.22)	0.06
HDL cholesterol level (per SD)	0.89 (0.79–1.01)	0.06
Lipoprotein(a) level > 0.90 mmol/L (> 25.3 mg/dL) in the placebo group§	1.44 (1.06–1.96)	0.02
Creatinine clearance ≤ 0.66 mL/s (≤ 40 mL/min)	1.56 (1.16–2.11)	0.004
≥ 2 previous myocardial infarctions	1.79 (1.22–2.62)	0.003
History or symptoms of CHF	1.33 (1.00–1.78)	0.05
Angina	1.49 (1.18–1.87)	< 0.001
Other		
Age (per 10 years)	1.13 (0.94–1.37)	0.19
Smoking		
Current	1.30 (0.92–1.84)	0.13
Past	0.99 (0.78–1.26)	> 0.2
Any alcohol use	0.97 (0.75–1.25)	> 0.2
Waist-to-hip ratio (per 0.10 unit)	1.03 (0.89–1.20)	> 0.2
Other diabetes¶	0.91 (0.60–1.36)	> 0.2
History of hypertension with normal blood pressure	1.18 (0.87–1.62)	> 0.2
Lipoprotein(a) level > 0.90 mmol/L (> 25.3 mg/dL) in the hormone therapy group**	0.97 (0.71–1.32)	> 0.2
Previous PTCA	0.94 (0.76–1.18)	> 0.2

* Coronary heart disease events include nonfatal myocardial infarction and death from coronary heart disease. Estimates are adjusted for assignment to hormone therapy and for use of statins, other lipid-lowering medications, aspirin, angiotensin-converting enzyme inhibitors, β -blockers, calcium antagonists, diuretics, and folate or vitamin B. The factors in Table 1 were considered for inclusion in the multivariable model; only body mass index and triglyceride level were excluded (see Methods). CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTCA = percutaneous coronary angioplasty.

† High blood pressure is defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

‡ The reference group is women who did not report a history of diagnosis and had a baseline glucose level ≤ 6.94 mmol/L (≤ 125 mg/dL).

§ The reference group is women assigned to placebo who had a lipoprotein(a) level ≤ 0.90 mmol/L (≤ 25.3 mg/dL).

|| Angina is defined by self-report as chest pain in the past 4 weeks during exercise, emotion, or sexual activity.

¶ Includes women reporting a history of diagnosis but no medication use and those with fasting plasma glucose levels > 6.94 mmol/L (> 125 mg/dL). The reference group is women who did not report a history of diagnosis and had a baseline glucose level ≤ 6.94 mmol/L (≤ 125 mg/dL).

** The reference group is women assigned to hormone therapy who had a lipoprotein(a) level at or below the median.

before enrollment. Twenty-six percent reported angina, and 12% had had heart failure. We found that those with two or more previous MIs and those with angina had substantially greater risk for subsequent CHD events. Congestive heart failure was also independently associated with CHD events. Because women with severe symptoms of heart failure were excluded from HERS, we may have underestimated the association of heart failure with coronary events in women with known coronary disease.

Table 3. Risk for Coronary Heart Disease Events and Use of Preventive Medications according to Number of Risk Factors*

Risk Factor†	Women n (%)	Annual CHD Event (95% CI)‡	Women Taking Aspirin and Other Antiplatelet Agents§		Women Taking β-Blockers		Women Taking ACE Inhibitors		Women Taking Lipid-Lowering Drugs	
			Baseline	End of the Study	Baseline	End of the Study	Baseline	End of the Study	Baseline	End of the Study
			%		%		%		%	
0	164 (6)	1.3 (0.7–2.5)	94	85	36	35	10	12	58	72
1	540 (20)	2.4 (1.9–3.2)	89	82	30	35	12	22	53	68
2	722 (26)	2.1 (1.7–2.7)	84	80	31	34	15	23	54	62
3	656 (24)	3.3 (2.6–4.1)	82	77	32	36	17	28	51	62
4	398 (14)	5.1 (4.1–6.4)	80	78	34	33	21	32	45	55
≥5	283 (10)	8.7 (7.1–10.8)	77	76	37	37	29	42	48	59
Overall	2763 (100)	3.4 (3.1–3.8)	83	79	33	35	18	28	53	66

* *P* value for trend in risk by number of risk factors is <0.001. ACE = angiotensin-converting enzyme; CHD = coronary heart disease.

† Number of risk factors includes lack of exercise, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, diabetes, low-density lipoprotein cholesterol level > 3.4 mmol/L (>130 mg/dL), high-density lipoprotein cholesterol level < 0.91 mmol/L (<35 mg/dL), lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL), nonwhite ethnicity, creatinine clearance ≤ 0.66 mL/s (≤40 mL/min), ≥2 previous myocardial infarctions, angina, and heart failure. These are the 11 risk factors identified as important in the multivariable model (Table 2). To evaluate the number of risk factors, low-density lipoprotein cholesterol level and high-density lipoprotein cholesterol level were dichotomized at established cut-points for elevated CHD risk.

‡ 95% CIs were computed under a Poisson assumption.

§ For aspirin and antiplatelet agents, the denominators excluded women using warfarin.

|| For lipid-lowering medications, the number of risk factors does not include levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or lipoprotein(a). Denominators excluded nonusers with normal lipid levels.

Whereas symptoms of angina and heart failure were associated with increased event rates, regular exercise was associated with decreased CHD events in HERS. This finding could represent the benefits of physical activity among women with CHD or simply reflect the greater propensity of healthy women to exercise. In contrast, we did not find obesity, defined either by body mass index or waist-to-hip ratio, to be a significant independent risk factor in HERS after adjustment for exercise and other covariates. However, because of the significant unadjusted association between obesity and CHD events and because it is a modifiable risk factor for high blood pressure and diabe-

tes, obesity is an appropriate target for secondary prevention efforts (29).

We identified two risk factors in HERS that are not as well known: reduced renal function and elevated lipoprotein(a) levels. Moderate renal insufficiency has been increasingly recognized as an independent predictor of cardiovascular events and death, but the mechanisms for the association are not clear (6, 21, 30, 31). Renal insufficiency has been linked both to the incidence of heart failure and to poor survival after heart failure (32, 33). Prevalence of moderate renal insufficiency, as defined by estimated creatinine clearance less than or equal to 0.66 mL/s (≤40

Table 4. Use of Indicated Medications by Risk Factor Status*

Risk Factor	Indicated Medication	All Women with the Risk Factor	Women with the Risk Factor Who Were Receiving the Indicated Medication
LDL cholesterol level ≥ 3.4 mmol/L (≥130 mg/dL)	Any lipid-lowering therapy Statins	2355 (85)†	1287 (55) 1004 (43)
History or symptoms of CHF	ACE inhibitors	345 (12)	128 (37)
Any previous MI	β-blockers Aspirin or other antiplatelet agent	1409 (51)	477 (34) 1134 (80)
≥2 previous MIs	β-blockers Aspirin or other antiplatelet agent	143 (5)	44 (31) 109 (76)
Angina without history of MI	β-blockers Aspirin or other antiplatelet agent	383 (14)	157 (41) 298 (78)
Creatinine clearance ≤ 0.66 mL/s (≤40 mL/min)	ACE inhibitors	323 (12)	78 (24)

* ACE = angiotensin-converting enzyme; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

† Includes women with normal LDL cholesterol level who were receiving lipid-lowering therapy.

mL/min), was 13% in the HERS cohort. This prevalence increases with age, making moderate renal insufficiency a risk factor of greater importance in this sample than in younger women (19).

Lipoprotein(a) levels were also a statistically significant risk factor, but only in the placebo group. The absence of an association between lipoprotein(a) level and CHD events in the active treatment group can probably be explained by the reduction in lipoprotein(a) levels caused by hormone therapy. We have previously shown that for women in HERS, reductions in lipoprotein(a) levels were independently associated with reduced rates of CHD events (21). Lipoprotein(a) level may prove to be an important consideration in secondary prevention efforts.

Despite the high CHD risk among HERS participants, the use of medications for secondary prevention was inadequate. In women with heart disease, treatment with aspirin, β -blockers, and lipid-lowering agents is one of the cornerstones of secondary prevention (22, 29, 34). One of the most important findings in HERS was the substantial underuse of these proven therapies (35, 36). Although most women in HERS were taking aspirin at enrollment, only one third were treated with β -blockers and only half of those who met NCEP II criteria for lipid-lowering therapy were using statins or other lipid-lowering treatments. Of concern, the women who had the greatest risk for CHD events in HERS were the least likely to be treated with aspirin or lipid-lowering medications. Furthermore, during the 4-year follow-up, use of β -blockers remained unchanged and use of aspirin and other antiplatelet agents decreased. Although use of statins increased during HERS, only two thirds of participants who met 1993 NCEP II criteria for treatment were taking lipid-lowering agents at the end of the study. Similarly low rates of utilization of these medications, as well as of other preventive interventions (ACE inhibitors, blood pressure and weight control, diet, exercise, and smoking cessation), have been observed in other clinical settings (37–44). In addition, women often receive less treatment than men (45–47). Proactive, targeted interventions should be developed to improve utilization of these preventive therapies (48).

The primary limitation of our study is that we examined voluntary participants in a secondary prevention trial. Our sample therefore may differ from the general population of women with coronary artery disease. Clinical trial participants tend to be healthier and more health conscious and therefore may be less in need of and more likely to engage in preventive behaviors. In addition, the enrollment criteria for HERS excluded the most infirm candidates, as evidenced by the lower-than-expected event rates (15). As a result, the significant associations we detected with dichotomous risk factors, including hypertension, diabetes, heart failure, and renal insufficiency, could represent underestimates. However, only 6% of women screened were excluded because of high serum levels of triglycerides, aspartate aminotransferase, or glucose (16).

The risk factor classifications that we considered important were to some extent data driven. This may inflate the type I error rates or the likelihood of mistakenly concluding that the observed associations are important. Our conclusion that LDL and HDL cholesterol levels are important risk factors was based on our interpretation of a multivariate *P* value of 0.06 in the context of information from other studies; other interpretations may also be valid. A further limitation is that the predictor variables measured in HERS did not include diagnostic tests, such as echocardiography and exercise testing, that might better predict clinical outcomes among women with coronary artery disease than risk factors for atherosclerosis. We also did not have good information on contraindications to medications, which may mean that our estimates of appropriate utilization are too low.

In conclusion, we used multivariable analysis to identify 11 easily assessed characteristics that predicted up to a sixfold increase in CHD events in a large sample of women who were already at high risk because they had coronary disease. This set of risk factors differs from those that have been established in primary prevention settings. In addition, we found substantial underuse of preventive treatments that have been established as beneficial, notably aspirin, β -blockers, and statins.

From the University of California, San Francisco, and Veterans Affairs Medical Center, San Francisco, California; Wake Forest University School of Medicine, Winston-Salem, North Carolina; University of California, Los Angeles, Los Angeles, California; Johns Hopkins University, Baltimore, Maryland; and University of California, San Diego, San Diego, California.

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Requests for Single Reprints: Eric Vittinghoff, PhD, University of California, San Francisco, 74 New Montgomery, Suite 600, San Francisco, CA 94105.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Vittinghoff, Ms. Ireland, and Dr. Hulley: University of California, San Francisco, 74 New Montgomery, Suite 600, San Francisco, CA 94105.

Drs. Shlipak and Varosy: Veterans Affairs Medical Center, 4150 Clement Street (111A1), San Francisco, CA 94121.

Dr. Furberg: Wake Forest University School of Medicine, One Medical Center Boulevard, Winston-Salem, NC 27157-1066.

Dr. Khan: Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 6215, Los Angeles, CA 90048-1804.

Dr. Blumenthal: Johns Hopkins University Hospital, 600 North Wolfe Street, Carnegie Room 538, Baltimore, MD 21287.

Dr. Barrett-Connor: University of California, San Diego, Stein Clinical Research Building 0607, CA 92093-0607.

Author Contributions: Conception and design: E. Vittinghoff, M.G. Shlipak, S. Hulley.

Analysis and interpretation of the data: E. Vittinghoff, M.G. Shlipak, P.D. Varosy, C.D. Furberg, S.S. Khan, S. Hulley.

Drafting of the article: E. Vittinghoff, M.G. Shlipak, P.D. Varosy, S.S. Khan, S. Hulley.

Critical revision of the article for important intellectual content: E. Vittinghoff, M.G. Shlipak, P.D. Varosy, C.D. Furberg, S.S. Khan, R. Blumenthal, E. Barrett-Connor, S. Hulley.

Final approval of the article: E. Vittinghoff, M.G. Shlipak, P.D. Varosy, C.D. Furberg, C.C. Ireland, S.S. Khan, R. Blumenthal, E. Barrett-Connor, S. Hulley.

Provision of study materials or patients: S.S. Khan, E. Barrett-Connor. Statistical expertise: E. Vittinghoff, P.D. Varosy.

Obtaining of funding: E. Barrett-Connor, S. Hulley.

Administrative, technical, or logistic support: C.D. Furberg, C.C. Ireland, S.S. Khan, S. Hulley.

Collection and assembly of data: S.S. Khan.