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Hypertension, Menopause, and Coronary Artery Disease Risk in the Women's Ischemia Syndrome Evaluation (WISE) Study

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OBJECTIVES We evaluated whether the relationship between hypertension, other cardiac risk factors, and coronary artery disease (CAD) is modulated by menopausal status and/or age.

BACKGROUND The relative contribution of age versus menopausal status in the development of CAD in women remains unclear.

METHODS We compared systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and traditional cardiac risk factors for CAD in premenopausal (n = 123) and postmenopausal (n = 482) women undergoing coronary angiography for suspected ischemia. To assess the relative contribution of age versus menopausal status, we fit a hypertension-menopausal status interaction term and adjusted for age.

RESULTS There were similar relationships with regard to traditional coronary risk factors and angiographic CAD in premenopausal versus postmenopausal women, with few exceptions. Twenty percent of premenopausal women had angiographic CAD versus 31% of postmenopausal women ($p = 0.02$). Premenopausal women had lower mean (standard deviation) SBP (132 [25] vs. 139 [20] mm Hg; $p < 0.0001$) and lower PP (54 [18] vs. 62 [18] mm Hg; $p < 0.0001$) compared to postmenopausal women; however, multivariable analyses revealed that SBP was a risk factor for CAD in premenopausal ($p = 0.002$) but not postmenopausal women ($p = 0.13$), and regression slopes were significantly different ($p = 0.04$). This interaction effect remained after age adjustment, suggesting independent risk contribution from both age and menopausal status. A similar slope difference was observed for PP ($p = 0.03$) but not for DBP.

CONCLUSIONS Among women undergoing angiography for suspected ischemia, elevated SBP and PP are potent risk factors in premenopausal women. The results suggest that identification of hypertension in premenopausal women dictates additional CAD risk factor assessment and management. (J Am Coll Cardiol 2006;47:50S–8S) © 2006 by the American College of Cardiology Foundation

The relationship between hypertension and heart disease is well established (1), and recent statements from the American Heart Association and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) have emphasized the importance of maintaining low blood pressure for prevention of heart disease and stroke (2,3). Specifically, renewed emphasis is being placed on detection and management of known risk factors for coronary artery disease (CAD) as early as age 20 years (2). Despite its high prevalence in the population, hypertension in women has received little attention in comparison to men (4–6). Beginning in adolescence and through middle age, men tend to exhibit higher mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) than women (7–10). However, a crossover in the prevalence of hypertension in men versus women, with older women having more hypertension than their age-matched male counterparts, has been reported in several epidemiologic studies (11) but not in others (12). Whether reproductive hormones account for this sexually dimorphic pattern of blood pressure remains a matter of controversy (13).

Recent data suggest that women develop high blood pressure, especially systolic hypertension, at an increased

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DBP = diastolic blood pressure
JNC = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
OR = odds ratio
PP = pulse pressure
SBP = systolic blood pressure
SD = standard deviation
WISE = Women's Ischemia Syndrome Evaluation

rate as they age (14). Furthermore, it has been noted that women develop CAD at a later age than men, particularly after menopause (15). For this reason, it has been suggested that the loss of reproductive hormones associated with postmenopausal status is a risk factor for both hypertension (16) and CAD (17–22). It is unclear, however, to what extent the increase in blood pressure and consequent CAD risk after reaching menopause represent hormonal changes versus simply advancing age. Recent clinical trials have raised more questions regarding the protective role of estrogen in CAD (23–27), and this phenomenon is still under debate (28–31).

Prior studies have suggested a more adverse prognosis after myocardial infarction in women compared to men (32–35), particularly among hypertensive women (5). This was attributed to older age and greater comorbidity burden (32), although recent data have shown that younger women with CAD evidence a more adverse prognosis compared to age-matched men (34,35). Specifically, Vaccarino et al. (34) demonstrated that among women under 50 years of age, the early myocardial infarction mortality rate was more than twice that for age-matched men (6.1% vs. 2.9%; $p < 0.001$ for interaction between age and gender). Assessment of CAD severity indicators, as well as medical treatment regimens did not readily explain this mortality difference (34).

Therefore, we evaluated the following research questions among women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study: 1) Are there important differences in blood pressure and other traditional cardiac risk factors between premenopausal and postmenopausal women? 2) Is blood pressure differently related to CAD in premenopausal versus postmenopausal women? And 3) If so, what is the relative contribution of menopausal status as opposed to age in modulating the relationship between hypertension and angiographic CAD?

MATERIALS AND METHODS

Study population. The study population consisted of 671 women clinically referred for coronary angiography for suspected myocardial ischemia and enrolled in the WISE study. The WISE study is a National Heart, Lung, and Blood Institute (NHLBI)-sponsored four-center study that aims to improve diagnostic testing and advance new hypotheses relative to the pathophysiology of ischemic heart disease in women. Study exclusion criteria included pregnancy, cardiomyopathy, New York Heart Association functional class IV congestive heart failure, recent myocardial infarction or revascularization, and any contraindications to provocative testing. Perimenopausal women (n = 49) and women with indeterminate menopausal status (n = 17) were not included in the present analysis. The complete study design and methodology of the WISE study have been described elsewhere (36).

For the analyses presented here, we examined 605 WISE study participants without a prior diagnosis of CAD, and with complete reproductive status and coronary angiographic data. The procedures followed were in accordance with each center's institutional guidelines, the study was approved by an institutional review committee at each site, and all participants gave informed consent.

Baseline evaluation. Women referred for coronary angiography for chest pain symptoms or suspected ischemia underwent an initial evaluation that included collection of demographic variables, medical history, physical activity, and psychosocial and symptom data. Participants underwent a physical examination that included heart rate, height, weight, body mass index, waist-hip ratio determination, and blood pressure evaluation. Lipoprotein determinations (triglycerides and total and high-density lipoprotein cholesterol) were performed at a lipid core laboratory enrolled in the Centers for Disease Control and Prevention lipid standardization program with experience in NHLBI-sponsored lipid-lowering intervention trials (37). Low-density lipoprotein cholesterol was estimated using the Friedewald formula (37).

Blood pressure evaluation. Blood pressure was measured following routine clinical standards as outlined by the JNC (38), using equipment that met certification criteria (39). The study nurse at each site began measurements after at least 5 min of rest; patients were seated, and both SBP and DBP were recorded. The first appearance of sound (phase 1) was used to define SBP. The disappearance of sound (phase 5) was used to define DBP. Two separate readings were taken and averaged. Pulse pressure (PP) was defined as the difference between SBP and DBP.

Determination of menopausal status. Reproductive hormone assays (E_2, bioavailable E_2, estrone, progesterone, follicle-stimulating hormone, and luteinizing hormone) were performed at the WISE reproductive hormone core laboratory from stored serum samples by an experienced technician (40). Validated steroid and protein assay methods were used, samples were assayed in batches of 100, and each determination was measured in duplicate. Consistent methodology was maintained for the duration of the study. Previous work from this laboratory has demonstrated that within- and between-assay coefficients of variation, respectively, were 15% and 16% for estrone, 8% and 12% for E_2,

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Table 1. Demographic, Coronary Risk Factor, and Medication Profile of WISE Women by Menopausal Status

Variable	Premenopausal (All, n = 123)	Postmenopausal (All, n = 482)	p Value	p Value, Age-Adjusted	Premenopausal (With CAD, n = 25)	Postmenopausal (With CAD, n = 149)	p Value	p Value, Age-Adjusted
Age, yrs, mean (SD)	43(6)	62(9)	<0.0001	—	46(5)	66(9)	<0.0001	—
Race (% white)	76	84	0.05	0.41	72	81	0.29	0.80
Current smoking (%)	27	17	0.01	0.002	28	16	0.16	0.06
History of DM (%)	20	20	0.85	0.37	44	31	0.22	0.26
History of hypertension (%)	47	57	0.06	0.26	64	64	0.98	0.62
History of dyslipidemia (%)	35	53	0.0008	0.47	41	67	0.02	0.09
Family history of premature CAD (%)	72	66	0.16	0.85	62	68	0.56	0.37
Lipid lowering (%)	13	22	0.02	0.30	20	32	0.21	0.83
Aspirin (%)	35	58	<0.0001	0.31	68	72	0.71	0.85
Beta-blockers (%)	35	31	0.37	0.05	52	34	0.09	0.22
Antihypertensive medications (%)*	27	46	0.0002	0.11	48	50	0.85	0.80
Insulin/oral (%)	17	16	0.98	0.59	40	25	0.11	0.25
Hormone therapy (%)	11	46	<0.0001	<0.0001	17	34	0.09	0.005

*Antihypertensive medications include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and vasodilators.
CAD = angiographic coronary artery disease defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery; DM = diabetes mellitus.

and 3.7% and 4.2% for bioavailable E_2 (41). Premenopausal and postmenopausal status were determined using a reproductive status algorithm developed for the WISE study that uses both reproductive historical variables and reproductive blood hormone levels to initially assign status, followed by expert consensus adjudication by a committee that included two reproductive endocrinologists (36,42).

Measurement of coronary angiography. Coronary angiograms were assessed by the WISE core laboratory used in previous multicenter trials with angiographic outcomes (43). Measurements included quantitative assessment of the presence, severity, and complexity of epicardial coronary artery stenosis, using previously published methods, and a coronary severity index (43). For these analyses, angiographic CAD was defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery, and multivessel CAD was defined as ≥50% luminal diameter stenosis in ≥2 epicardial coronary arteries.

Statistical analysis. Comparisons between premenopausal and postmenopausal women were performed by the Wilcoxon rank sum test for continuous measures and by the chi-square test for discrete measures. Fisher exact test for discrete measures was used when expected cell counts were <5. Age-adjusted p values were obtained by logistic or linear regression, where appropriate. In general, when multivariable comparisons were significant but became nonsignificant when adjusted for age, the difference was considered age related. When multivariable comparisons were nonsignificant but became significant when adjusted for age, the difference was considered menopausal status related. When unadjusted and adjusted comparisons were both significant, the difference was considered independently related to both age and menopausal status. Finally, to determine the independent association between the hypertension variables and CAD, we used stepwise multivariable logistic regression analysis to model angiographic CAD as a function of the hypertension variables and menopausal status. The differential impact of menopausal status on these relationships was examined by fitting a risk factor/menopausal status interaction term. Probability values of ≤0.05 were considered statistically significant. All tests of statistical significance were two tailed. Analyses were performed using SAS software release 8.0 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics. Among the 605 WISE study participants without a prior diagnosis of CAD, and with complete demographic, reproductive status, and coronary angiographic data, the mean (SD) age was 58 (11) years, ranging from 21 to 85 years; 18% were racial minorities (primarily African American); and 80% were postmenopausal. In this population, there was a high prevalence of CAD risk factors, including diabetes (20%), dyslipidemia (49%), hypertension (55%), history of smoking (50%), and obesity (mean [SD] body mass index = 29.9 [7]). Despite this prevalent coronary risk factor load, only 174 (29%) of these women had angiographic CAD, including 25 (20%) premenopausal and 149 (31%) postmenopausal women.

Comparisons of premenopausal versus postmenopausal women. Comparative demographic, coronary risk factor, and medication variables by premenopausal versus postmenopausal women are shown in Tables 1 and 2. As expected, premenopausal women were significantly younger compared to the postmenopausal women: mean (SD, range) 43 (6, 21 to 54) versus 62 (9, 36 to 85); $p < 0.0001$. Among the overall population, there were no significant group differences in coronary risk factors after adjusting for age, with the exception of current smoking which was more prevalent in premenopausal women (27% vs. 17% in the

Table 2. Coronary Risk Factor Profile for WISE Women by Menopausal Status

Variable	All WISE Women (n = 605)	Premenopausal (All, n = 123)	Postmenopausal (All, n = 482)	p Value	p Value, Age-Adjusted	WISE women (With CAD, n = 174)	Premenopausal (With CAD, n = 25)	Postmenopausal (With CAD, n = 149)	p Value	p Value, Age-Adjusted
Fasting glucose (mg/dl)	111 (46)	114 (57)	109 (42)	0.72	0.67	118 (52)	116 (40)	118 (54)	0.70	0.80
Total cholesterol (mg/dl)	194 (45)	182 (46)	197 (44)	0.0002	0.001	199 (49)	178 (43)	203 (50)	0.02	0.02
Triglycerides (mg/dl)	140 (87)	128 (85)	143 (87)	0.03	0.31	154 (92)	127 (64)	159 (96)	0.19	0.41
LDL-C (mg/dl)	113 (39)	106 (37)	115 (40)	0.01	0.02	118 (44)	107 (40)	120 (45)	0.21	0.09
HDL-C (mg/dl)	54 (12)	50 (10)	55 (13)	0.003	0.02	52 (11)	48 (14)	52 (10)	0.04	0.30
BMI	29.9 (6.7)	30.8 (6.7)	29.6 (6.6)	0.05	0.36	29.1 (6.1)	29.9 (4.9)	29.0 (6.2)	0.36	0.96
WHR	0.85 (0.10)	0.84 (0.08)	0.85 (0.11)	0.49	0.75	0.87 (0.09)	0.88 (0.07)	0.87 (0.09)	0.38	0.34
SBP (mm Hg)*	137 (22)	132 (25)	139 (20)	<0.0001	0.19	141 (24)	147 (35)	141 (21)	0.57	0.03
DBP (mm Hg)*	77 (11)	77 (12)	76 (10)	0.50	0.87	77 (12)	81 (15)	76 (11)	0.26	0.56
Pulse pressure (mm Hg)†	61 (18)	54 (18)	62 (18)	<0.0001	0.08	65 (20)	66 (27)	64 (19)	0.56	0.02

Values are mean (SD). *Data are missing for one premenopausal and three postmenopausal women. †Pulse pressure calculated as SBP − DBP; data are missing for one premenopausal and four postmenopausal women.
BMI = body mass index, calculated as weight (kg)/height^2 (m); CAD = angiographic coronary artery disease defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; SD = standard deviation; WHR = waist-hip ratio.

postmenopausal group), both unadjusted (p = 0.01) and adjusted for age (p = 0.002). Furthermore, there were no age-adjusted differences in measured blood pressure, waist-hip ratio, fasting blood sugar, and body mass index. However, the premenopausal women had lower age-adjusted total cholesterol (p = 0.001) and low-density lipoprotein cholesterol (p = 0.02), but also lower high-density lipoprotein cholesterol (p = 0.02) than the postmenopausal women (Table 2). Although postmenopausal women were more likely to use aspirin, lipid-lowering, and antihypertensive medications, these differences disappeared when adjusting for age, suggesting an age-related prevalence of such medication use (Table 1).

The prevalence of angiographic CAD by menopausal status is shown in Table 3. Despite their largely similar age-adjusted coronary risk factor profiles, premenopausal women had a lower yet substantial prevalence of angiographic CAD as compared to postmenopausal women (20% vs. 31%). Similarly, the mean CAD severity index was significantly higher in postmenopausal women (p < 0.0001). These differences remained significant after age adjustment (p = 0.01). Premenopausal and postmenopausal women did not differ in the actual prevalence of multivessel angiographic CAD (p = 0.17); however, a significant difference emerged after adjustment for age (p = 0.02).

We next evaluated the subgroup (n = 174) of WISE study women with angiographic CAD, defined as ≥50% stenosis in ≥1 epicardial coronary artery. Although the overall demographics and risk factor differences between premenopausal and postmenopausal women remained the same, a major reversal was noted in the hypertension variables. Premenopausal women with angiographic CAD exhibited a higher SBP (147 [35] vs. 141 [21] mm Hg) and PP (66 [27] vs. 64 [19] mm Hg) than their postmenopausal counterparts, a difference that became significant after age adjustment (p = 0.03 and 0.02, respectively) (Table 2). The premenopausal and postmenopausal women with angiographic CAD had similar age-adjusted usages of lipid-lowering, aspirin, beta-blocker, and antihypertensive medications, and hormone therapy use, not surprisingly, was significantly higher in the postmenopausal women (p = 0.005).

Among this subgroup, comparison of the severity of multivessel angiographic CAD status by menopausal status demonstrated that premenopausal women had a relatively similar prevalence of multivessel CAD (48% vs. 49% of postmenopausal women) and a similar mean (range) coronary severity index to that of the postmenopausal women (24 [5 to 78] vs. 27 [5 to 78]). Age adjustment did not significantly alter these results.

Multivariable analyses. To describe the presence of CAD, the explanatory variables of age, race, current smoking, blood lipoprotein levels, SBP, PP, and body mass index were considered with the following results: Among the overall population, age was the most significantly associated with CAD (odds ratio [OR] 1.05, 95% confidence interval

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Table 3. Prevalence of Angiographic CAD for WISE Women by Menopausal Status

Variable	All WISE Women (n = 605)	Premenopausal (All, n = 123)	Postmenopausal (All, n = 482)	p Value	p Value, Age-Adjusted
CAD (%)	29	20	31	0.02	0.02
Multivessel CAD (%)	14	10	15	0.17	0.02
Coronary severity index, mean (SD)	12 (13)	9 (11)	13 (13)	<0.0001	0.01

CAD = angiographic coronary artery disease defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery; Multivessel CAD = ≥50% stenosis in ≥2 epicardial coronary arteries.

[CI] 1.03 to 1.07; $p < 0.0001$), such that for every 10-year increment in age an associated 66% elevation in the presence of angiographic CAD resulted (95% CI 1.36 to 2.03).

Whether menopausal status modulates the relationship between hypertension and angiographic CAD was then explored. Angiographic CAD was modeled as a function of hypertension, menopausal status, and the interaction between hypertension and menopausal status among the 605 WISE study participants; the model was then adjusted for age. A significant differential impact of menopausal status was detected with respect to SBP and PP but not to DBP. Although SBP was lower in the premenopausal women (Table 2), regression analyses including the interaction between SBP and menopausal status demonstrated that SBP was paradoxically a more potent risk factor for CAD in the premenopausal women ($p = 0.002$) than in the postmenopausal women ($p = 0.13$), and the regression slopes were significantly different ($p = 0.04$ for interaction) (Table 4, Fig. 1A). For every 10-mm Hg increase in SBP, the odds of CAD for premenopausal women increased 35% (95% CI 1.11 to 1.64; $p = 0.002$), whereas the odds for postmenopausal women increased 7% (95% CI 0.98 to 1.18; $p = 0.13$). This significant interaction effect remained even after adjusting for age ($p = 0.02$). Controlling for race, antihypertensive medications and hormone therapy also did not affect results ($p = 0.02$; data not shown). A similar slope difference was observed for PP ($p = 0.03$ for interaction) (Table 4, Fig. 1B) but not for DBP ($p = 0.13$). For every 10-mm Hg increment in PP, the odds of CAD for premenopausal women increased 48% (95% CI 1.16 to 1.90; $p = 0.001$), whereas the odds of CAD for postmenopausal women increased 10% (95% CI 0.99 to 1.23; $p = 0.07$). Again, the interaction remained significant after adjustment for age ($p = 0.01$) (Table 4), and controlling for race, antihypertensive treatment, and hormone therapy use did not further influence results ($p = 0.01$; data not shown). The age-adjusted models shown in Table 4 were evaluated for linear relationships among variables in the model (collinearity) which have the potential of rendering significance testing unreliable. Using standard diagnostic techniques (44), these models were found to be fairly reliable (tolerance = 0.58; condition index = 14.7), suggesting mild collinearity between age and menopausal status.

In order to describe the presence of CAD in premenopausal and postmenopausal women separately, the explanatory variables of age, race, current smoking, blood lipoprotein levels, SBP, PP, and body mass index were considered in subgroup analyses. Results for postmenopausal women were similar to those of the overall population: age remained the variable most significantly associated with CAD (OR 1.07, 95% CI 1.04 to 1.10; $p < 0.0001$). However, for premenopausal women SBP emerged as the most powerful risk factor even after adjusting for the other CAD risk factors (OR 1.02, 95% CI 1.005 to 1.05; $p = 0.01$). Specifically, in the premenopausal women, cigarette smoking did not have a main effect on CAD prevalence or severity.

To interpret these results within the context of current clinical standards, the JNC VII criterion for hypertension was applied. The JNC VII defines systolic hypertension in adults age 18 years or over as SBP ≥140 mm Hg (3). Among premenopausal WISE study women, 26% (n = 32) had an SBP of 140 or higher at their baseline evaluation. The odds of angiographically defined CAD were 5.6 times higher among those premenopausal women who had an SBP ≥140 mm Hg, (OR 5.59, 95% CI 2.18 to 14.31) as compared to premenopausal women with SBP <140 mm Hg, and this result was statistically significant ($p = 0.0003$). Although a substantial proportion of hypertensive premenopausal women reported a history of diabetes (47%), the odds of CAD were still substantially increased for premenopausal women with SBP ≥140 mm Hg after adjustment for history of diabetes and antihypertensive medication use (OR 3.37, 95% CI 1.19 to 9.53; $p = 0.02$).

DISCUSSION

Among women undergoing coronary angiography for suspected myocardial ischemia, premenopausal women had a substantial prevalence of CAD despite their relatively lower risk profile. Prior work in younger CAD patients has primarily focused on men (45), although premenopausal women represent about 20% of all CAD deaths among women annually (46). Notably, the current study results established that the age-adjusted prevalence of multivessel CAD was virtually equivalent in the subgroups of premenopausal and postmenopausal women with angiographic CAD.

These findings demonstrated relatively similar relationships between traditional coronary risk factors and angiographic CAD in premenopausal versus postmenopausal women, with few exceptions. Although the premenopausal women were more likely to be smokers, smoking did not have a main effect on angiographic disease prevalence or

Table 4. All WISE Women: Variation of the Effect of Menopausal Status, Systolic Blood Pressure, and Pulse Pressure on the Presence of CAD, Adjusted and Unadjusted for Age

Model	Increase in Odds of CAD (95% CI)	p Value	Age-Adjusted Increase in Odds of CAD (95% CI)	p Value, Age-Adjusted
SBP (mm Hg)*	1.03 (1.01–1.05)	0.002	1.03 (1.01–1.04)	0.008
MP status‡	38.16 (1.87–776.52)	0.02	12.92 (0.64–260.7)	0.10
SBP × MP status	0.98 (0.96–0.99)	0.04	0.97 (0.95–1.0)	0.02
Age	—	—	1.08 (1.05–1.1)	<0.0001
Max-rescaled R^2	0.04		0.14	
Goodman-Kruskal *c*	0.58		0.69	
PP (mm Hg)†	1.04 (1.01–1.07)	0.001	1.03 (1.01–1.06)	0.006
MP status‡	8.98 (1.67–48.04)	0.01	3.15 (0.57–17.26)	0.19
PP × MP status	0.97 (0.94–1.0)	0.03	0.97 (0.94–0.99)	0.01
Age	—	—	1.08 (1.05–1.1)	<0.0001
Max-rescaled R^2	0.05		0.14	
Goodman-Kruskal *c*	0.59		0.69	

*Data are missing for one premenopausal and three postmenopausal women. †Data are missing for one premenopausal and four postmenopausal women. ‡Menopausal status was coded as 0 for premenopausal and 1 for postmenopausal women. Age, SBP, and PP were included as continuous variables.

CAD = angiographic coronary artery disease defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery; CI = confidence interval; MP = menopausal; PP = pulse pressure; SBP = systolic blood pressure.

severity; this lack of association could be due to the relatively small number of premenopausal women with prevalent CAD. Although prior reports have emphasized the high prevalence of cigarette smoking and single-vessel disease in relatively young CAD patients (45,47,48), these reports have focused on myocardial infarction patients and therefore may represent a selection bias in favor of acute thrombotic events as opposed to the coronary artery atherosclerotic process.

There were no differences in the multivariable models of coronary risk factors that were attributable to age versus menopause, possibly due to mild collinearity between these two variables. Age-adjusted differential relationships between PP and SBP and menopausal status were found in the WISE study population. Both interaction effects remained significant even after adjustment for age, suggesting independent risk contribution from both age and menopausal status. The influence of menopause on blood pressure in women is not well understood. Blood pressure changes associated with menopause are difficult to evaluate, because menopause coincides with aging. In an observational study of ~11,000 women in Italy, menopause had no predictive role and was rejected from the multivariable equations of risk, with cardiovascular risk being completely explained by age and blood pressure (30). Prospective cohort studies have not found an increase in blood pressure with menopause (18, 49–53); however, results from cross-sectional studies have been equivocal, with some studies finding significantly higher SBP and DBP in postmenopausal than in premenopausal women (14, 54–57) and other studies finding little or no association (58,59). In contrast, among the WISE study women with angiographic CAD, premenopausal women presented with significantly higher SBP and PP than their postmenopausal counterparts.

Moreover, estimating the interaction effect between blood pressure and menopausal status in the overall cohort demonstrated that both SBP and PP were more potent risk factors for CAD in the premenopausal group. Whereas

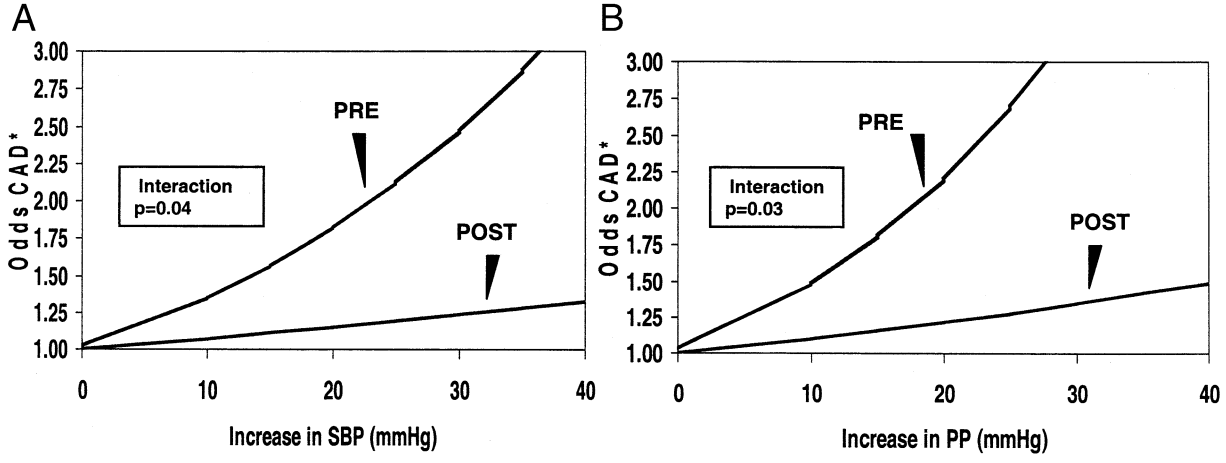

Figure 1. Increasing (**A**) systolic blood pressure (SBP, mm Hg) and (**B**) pulse pressure (PP, mm Hg) and odds of coronary artery disease (CAD) in premenopausal (PRE) and postmenopausal (POST) women. *CAD = angiographic coronary artery disease defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery.

prior research has found that DBP values are the strongest predictor of coronary heart disease risk in younger men (60), measures of SBP may be a strong prognostic factor of carotid artery atherosclerosis in premenopausal women (61). Recent data from the Healthy Women Study demonstrated that premenopausal SBP and PP were predictive of carotid intimal-medial thickness and plaque 5 to 8 years after menopause (61), suggesting that premenopausal levels of SBP and PP may identify high-risk younger women. The WISE study has confirmed these findings in a different population of women with suspected angiographic CAD.

Despite having relatively similar age-adjusted risk factor loads, unadjusted aspirin and antihypertensive medication usage was lower among the premenopausal women, although this unadjusted difference was no longer evident among women with angiographic CAD. In addition, the difference in antihypertensive therapy between premenopausal and postmenopausal women did not account for the significant interaction effects between PP, SBP, and menopausal status. Still, a minority of women in our population with evident CAD were treated with appropriate medications. Prior analyses have indicated that a variety of cardiovascular treatments are underutilized and understudied in women as compared with men (62–64), although controversy exists regarding the appropriateness of this treatment pattern (65). Current guidelines for the diagnosis and treatment of hypertension are not gender specific (3), and few studies have examined treatment by either age or menopausal status (13,34). However, younger women have typically been excluded from most antihypertensive trials owing to potential teratogenicity of medications and a prevalence of hypertension lower than that in men through middle age (9,13).

Eleven percent of premenopausal women from the present study reported a history of hormone therapy use. Menstrual irregularities in these women could be one explanation for their prescribed hormone therapy. As previously reported (66), a substantial proportion of the premenopausal WISE study women have reproductive hormone profiles and symptoms consistent with hypothalamic hypoestrogenemia, often with associated anovulatory cycles and amenorrhea.

Novel risk factors, including central estrogen deficiency and anovulatory status (66), should therefore be investigated as both a mechanism of CAD in premenopausal women and a pathophysiologic participant in the relatively more adverse outcomes experienced in premenopausal women than in age-matched men (34). Indeed, disruption of ovulatory cycling characterized by hypoestrogenemia of hypothalamic origin was associated with angiographic CAD among the premenopausal WISE study women in a prior study (66). Central estrogen deficiency in premenopausal women could potentially impact SBP and PP through a variety of mechanisms. Recent epidemiologic and experimental evidence indicate that estrogen deficiency may cause increases in SBP and elevated PP through impacting endothelial vascular function and/or systemic arterial compliance (13,16,67,68). This hypothesis warrants further investigation.

Study limitations. The current study results are limited by our cross-sectional design which precludes inference regarding causality between hypertension, additional coronary risk factors, and angiographic CAD. Also, although angiographically confirmed CAD represents an advantage over noninvasive cardiovascular markers, this study is limited in its capacity to link these coronary risk factor analyses to adverse coronary events, such as coronary mortality. Use of a clinically referred coronary angiography population also reduces our ability to detect relationships between risk factors and angiographic CAD, owing to a selection bias whereby participants with risk factors are preferentially referred for angiography. In addition, the subgroup analyses are limited by our small sample size of premenopausal women with CAD, and the multivariable analyses may be limited by mild collinearity between age and menopausal status. Finally, the WISE study population of women, selected because they were undergoing coronary angiography for suspected myocardial ischemia, may not be representative of the relationships between menopausal status, coronary risk factors, and CAD in the general population of women. However, the WISE study cohort includes women who exhibit a broad range of angiographically documented CAD. This study design provides a unique opportunity to evaluate associations among blood pressure, other traditional cardiac risk factors, and angiographic CAD in premenopausal and postmenopausal women.

Conclusions. Among women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia, 20% of premenopausal women had angiographic CAD versus 31% of postmenopausal women. Blood pressure was differentially related to CAD according to menopausal status, with high SBP and PP constituting a higher risk in premenopausal versus postmenopausal women. This increased risk was not attributable to age alone. These results suggest that identification of hypertension in premenopausal women should dictate additional CAD risk assessment and risk factor management. Further research aimed at better understanding blood pressure, CAD risk, and therapeutics within the context of prospective measures of endogenous hormones is needed if we are to optimize CAD outcomes in premenopausal women.

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REFERENCES

1. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003;290:891–7.

2. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. Circulation 2002;106:388–91.
3. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–71.
4. Kaplan NM. The treatment of hypertension in women. Arch Intern Med 1995;155:563–7.
5. Robitaille NM. Hypertension in women. Can J Cardiol 1996;12 Suppl D:6D–8D.
6. Calhoun DA, Oparil S. High blood pressure in women. Int J Fertil Womens Med 1997;42:198–205.
7. Yong LC, Kuller LH, Rutan G, et al. Longitudinal study of blood pressure: changes and determinants from adolescence to middle age. The Dormont High School follow-up study. 1957–1963 to 1989–1990. Am J Epidemiol 1993;138:973–83.
8. Himmelmann A, Svensson A, Hansson L. Influence of sex on blood pressure and left ventricular mass in adolescents: the Hypertension in Pregnancy Offspring Study. J Hum Hypertens 1994;8:485–90.
9. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the third National Health and Nutrition Examination Survey. 1988–1991. Hypertension 1995;25:305–13.
10. Calhoun DA, Oparil S. The sexual dimorphism of high blood pressure. Cardiol Rev 1998;6:356–63.
11. Kotchen JM, McKean HE, Kotchen TA. Blood pressure trends with aging. Hypertension 1982;4:III128–34.
12. Vokonas PS, Kannel WB, Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham study. J Hypertens 1988;6:S3–9.
13. Rosenthal T, Oparil S. Hypertension in women. J Hum Hypertens 2000;14:691–704.
14. Staessen JA, Ginocchio G, Thijs L, et al. Conventional and ambulatory blood pressure and menopause in a prospective population study. J Hum Hypertens 1997;11:507–14.
15. Kannel WB, Hjortland MC, McNamara PM, et al. Menopause and risk of cardiovascular disease: the Framingham study. Ann Intern Med 1976;85:447–52.
16. Rajkumar C, Kingwell BA, Cameron JD, et al. Hormonal therapy increases arterial compliance in postmenopausal women. J Am Coll Cardiol 1997;30:350–6.
17. Gordon T, Kannel WB, Hjortland MC, et al. Menopause and coronary heart disease. The Framingham study. Ann Intern Med 1978;89:157–61.
18. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111:383–90.
19. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316:1105–10.
20. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA 1991;265:1861–7.
21. van der Schouw YT, van der Graaf Y, Steyerberg EW, et al. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714–8.
22. Gensini GF, Comeglio M, Colella A. Classical risk factors and emerging elements in the risk profile for coronary artery disease. Eur Heart J 1998;19 Suppl A:A53–61.
23. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–13.
24. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). JAMA 2002;288:49–57.
25. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
26. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523–34.
27. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–12.
28. McKinlay JB. Some contributions from the social system to gender inequalities in heart disease. J Health Soc Behav 1996;37:1–26.
29. Mercuro G, Zoncu S, Cherchi A, et al. Can menopause be considered an independent risk factor for cardiovascular disease? Ital Heart J 2001;2:719–27.
30. Casiglia E, Tikhonoff V, Mormino P, et al. Is menopause an independent cardiovascular risk factor? Evidence from population-based studies J Hypertens 2002;20 Suppl 2:S17–22.
31. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002;288:872–81.
32. Tofler GH, Stone PH, Muller JE, et al. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol 1987;9:473–82.
33. Greenland P, Reicher-Reiss H, Goldbourt U, et al. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. Circulation 1991;83:484–91.
34. Vaccarino V, Parsons L, Every NR, et al. Sex-based differences in early mortality after myocardial infarction. N Engl J Med 1999;341:217–25.
35. Vaccarino V, Krumholz HM, Yarzebski J, et al. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. Ann Intern Med 2001;134:173–81.
36. Bairey Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. J Am Coll Cardiol 1999;33:1453–61.
37. Lipid Research Clinics Program. The Manual of Laboratory Operations: Lipid and Lipoprotein Analysis. Bethesda, MD: National Institutes of Health DHEW, 1974.
38. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413–46.
39. Prisant LM, Alpert BS, Robbins CB, et al. American national standard for nonautomated sphygmomanometers: summary report. Am J Hypertens 1995;8:210–3.
40. Anderson DC, Hopper BR, Lasley BL, et al. A simple method for the assay of eight steroids in small volumes of plasma. Steroids 1976;28:179–96.
41. Barrett-Connor E, Goodman-Gruen D. Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. BMJ 1995;311:1193–6.
42. Johnson BD, Bairey Merz CN, Braunstein GD, et al. Determination of menopausal status in women: the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study. J Womens Health 2004;13:872–87.
43. Sharaf BL, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] study angiographic core laboratory). Am J Cardiol 2001;87:937–41.
44. Belsey A, Kuh E, Welsch RE. Regression Diagnostics: Identifying Influential Data and Sources of Collinearity. New York, NY: John Wiley and Sons, 1980.
45. Choudhury L, Marsh JD. Myocardial infarction in young patients. Am J Med 1999;107:254–61.
46. Statistical Abstract of the United States. 112th ed. Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, 1992.
47. Hoit BD, Gilpin EA, Henning H, et al. Myocardial infarction in young patients: an analysis by age subsets. Circulation 1986;74:712–21.
48. Zimmerman FH, Cameron A, Fisher LD, et al. Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study registry). J Am Coll Cardiol 1995;26:654–61.
49. Hjortland MC, McNamara PM, Kannel WB. Some atherogenic concomitants of menopause: the Framingham study. Am J Epidemiol 1976;103:304–11.
50. Lindquist O. Intraindividual changes of blood pressure, serum lipids, and body weight in relation to menstrual status: results from a

prospective population study of women in Goteborg, Sweden. Prev Med 1982;11:162–72.
51. Matthews KA, Meilahn E, Kuller LH, et al. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641–6.
52. van Beresteyn EC, van't Hof MA, De Waard H. Contributions of ovarian failure and aging to blood pressure in normotensive perimenopausal women: a mixed longitudinal study. Am J Epidemiol 1989;129: 947–55.
53. Van Beresteijn EC, Riedstra M, van der Wel A, et al. Habitual dietary calcium intake and blood pressure change around the menopause: a longitudinal study. Int J Epidemiol 1992;21:683–9.
54. Weiss NS. Relation of high blood pressure to headache, epistaxis, and selected other symptoms. The United States Health Examination Survey of Adults. N Engl J Med 1972;287:631–3.
55. Eferakeya AE, Imasuen JE. Relationship of menopause to serum cholesterol and arterial blood pressure in some Nigerian women. Public Health 1986;100:28–32.
56. Staessen J, Bulpitt CJ, Fagard R, et al. The influence of menopause on blood pressure. J Hum Hypertens 1989;3:427–33.
57. Portaluppi F, Pansini F, Manfredini R, et al. Relative influence of menopausal status, age, and body mass index on blood pressure. Hypertension 1997;29:976–9.
58. Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: results from a population study of women in Goteborg, Sweden. Scand J Clin Lab Invest 1980;40:629–36.
59. Wu Z, Wu X, Zhang Y. Relationship of menopausal status and sex hormones to serum lipids and blood pressure. Int J Epidemiol 1990;19:297–302.
60. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study (comment). Circulation 2001;103:1245–9.
61. Matthews KA, Kuller LH, Sutton-Tyrrell K, et al. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. Stroke 2001;32:1104–11.
62. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease. Survival and Ventricular Enlargement Investigators. N Engl J Med 1991;325:226–30.
63. Krumholz HM, Douglas PS, Lauer MS, et al. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: Is there evidence for a gender bias? Ann Intern Med 1992;116:785–90.
64. Gueyffier F, Boutitie F, Boissel JP, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997;126:761–7.
65. Bickell NA, Pieper KS, Lee KL, et al. Referral patterns for coronary artery disease treatment: gender bias or good clinical judgment? Ann Intern Med 1992;116:791–7.
66. Bairey Merz CN, Johnson BD, Sharaf BL, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. J Am Coll Cardiol 2003;41:413–9.
67. Taddei S, Virdis A, Ghiadoni L, et al. Menopause is associated with endothelial dysfunction in women. Hypertension 1996;28:576–82.
68. Staessen JA, Celis H, Fagard R. The epidemiology of the association between hypertension and menopause. J Hum Hypertens 1998;12: 587–92.