Postmenopausal Women with a History of Irregular Menses and Elevated Androgen Measurements at High Risk for Worsening Cardiovascular Event-Free Survival: Results from the National Institutes of Health—National Heart, Lung, and Blood Institute Sponsored Women's Ischemia Syndrome Evaluation

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Background: Women with polycystic ovary syndrome (PCOS) have a greater clustering of cardiac risk factors. However, the link between PCOS and cardiovascular (CV) disease is incompletely described.

Objective: The aim of this analysis was to evaluate the risk of CV events in 390 postmenopausal women enrolled in the National Institutes of Health–National Heart, Lung, and Blood Institute (NIH-NHLBI) sponsored Women's Ischemia Syndrome Evaluation (WISE) study according to clinical features of PCOS.

Methods: A total of 104 women had clinical features of PCOS defined by a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenemia. Hyperandrogenemia was defined as the top quartile of androstenedione (≥701 pg/ml), testosterone (≥30.9 ng/dl), or free testosterone (≥4.5 pg/ml). Cox proportional hazard model was fit to estimate CV death or myocardial infarction (n = 55).

Results: Women with clinical features of PCOS were more often diabetic ($P < 0.0001$), obese ($P = 0.005$), had the metabolic syndrome ($P < 0.0001$), and had more angiographic coronary artery disease (CAD) ($P = 0.04$) compared to women without clinical features of PCOS. Cumulative 5-yr CV event-free survival was 78.9% for women with clinical features of PCOS (n = 104) *vs.* 88.7% for women without clinical features of PCOS (n = 286) ($P = 0.006$). PCOS remained a significant predictor ($P < 0.01$) in prognostic models including diabetes, waist circumference, hypertension, and angiographic CAD as covariates.

Conclusion: Among postmenopausal women evaluated for suspected ischemia, clinical features of PCOS are associated with more angiographic CAD and worsening CV event-free survival. Identification of postmenopausal women with clinical features of PCOS may provide an opportunity for risk factor intervention for the prevention of CAD and CV events. **(*J Clin Endocrinol Metab* 93: 1276–1284, 2008)**

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Abbreviations: CAD, Coronary artery disease; CI, confidence interval; CV, cardiovascular; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; PCOS, polycystic ovary syndrome.

The higher sex-specific coronary mortality observed in women compared with men (1–5), combined with a greater proportion of women in the population, has resulted in relatively more women dying of cardiovascular (CV) disease each year than men (6). Realization of the magnitude of this problem has led to targeted investigations designed to further our understanding of the mechanisms of CV disease in women.

Endogenous sex hormones including estrogen are hypothesized as the primary reason for the lower incidence of CV disease among normal ovulatory premenopausal women compared with age-matched men and the subsequent age-related rise in women postmenopausally (7–11). Conversely, clustering of traditional risk factors in polycystic ovary syndrome (PCOS), a prevalent disorder associated with androgen excess, could elevate CV disease risk in women similar to that of age-matched men.

Despite risk factor clustering, studies published to date have failed to demonstrate a uniform association between PCOS and CV disease (12–14). An apparent lack of association between PCOS and CV disease may be due to inadequate PCOS characterization, inadequate CV disease measurement, insufficient duration of follow-up, or a true lack of association. Accordingly, we tested the hypothesis that women with clinical features of PCOS more often had angiographic coronary artery disease (CAD) and CV disease events in a carefully characterized group of postmenopausal women enrolled in the National Institutes of Health (NIH)–National Heart, Lung, and Blood Institute (NHLBI) sponsored Women's Ischemia Syndrome Evaluation (WISE).

Patients and Methods

Patient entry criteria

The WISE is a four-center study with key objectives to improve diagnostic testing for ischemic heart disease in women and to study pathophysiological mechanisms and prognosis in women with symptoms and evidence of myocardial ischemia in the absence or presence of obstructive CAD. Participating enrolling centers included the University of Alabama at Birmingham, University of Florida, University of Pittsburgh, and Allegheny Medical Center in Pittsburgh. Women enrolled in the WISE underwent a clinically indicated coronary angiogram for suspected ischemia, yet with stable cardiac symptoms.

Among the 855 WISE participants with complete demographic, reproductive status, and coronary angiographic data, 390 (42%) were postmenopausal and non-hormone therapy and non-oral contraceptive users. A total of 54 of the 390 postmenopausal women had bilateral oopherectomy. Analyses excluding these women did not alter the current results.

Baseline data collection

All WISE patients underwent a physical examination that included measures of heart rate, blood pressure, height, weight, waist and hip circumference, body mass index, and detailed past medical history. Cardiac risk factors were defined according to the definitions of the National Cholesterol Education Program, Adult Treatment Panel III (15). More detailed information on the WISE study design has been published (16). Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) index with a threshold of at least 2.5 (17).

Androgen, lipoprotein, and high-sensitivity C-reactive protein assays

Androstenedione and total testosterone were quantified in serum by previously described and validated RIAs (18, 19). Before RIA, androstenedione and testosterone were extracted with hexane:ethyl acetate (3:2) and purified by Celite column partition chromatography, using ethylene glycol as stationery phase. Elution of androstenedione and testosterone off the column was carried out by use of isooctane and 40% toluene in isooctane, respectively. The intraassay coefficients of variation for androstenedione and testosterone were 6.0% at 0.40 ng/dl and 7.0% at 14.3 ng/dl, respectively. The interassay coefficients of variation for androstenedione were 7.8, 8.9, and 7.3% at 0.13, 0.41, and 1.37 ng/ml, respectively, and for testosterone they were 10.4, 10.0, and 8.9% at 6.1, 15.4, and 49.4 ng/dl, respectively.

The sensitivities of the androstenedione and testosterone assays were 0.030 ng/ml and 1.5 ng/dl.

Free testosterone concentration in a given sample was calculated using the measured total testosterone and SHBG concentrations in the same sample and an assumed constant concentration of albumin (20, 21). The validity of the calculation method for determining free testosterone concentrations has been reported (22).

Lipoprotein determinations were performed at a lipid core laboratory enrolled in the Centers for Disease Control and Prevention lipid standardization program and previously used in multiple NHLBI-sponsored lipid-lowering intervention trials using the Friedewald formula (23). The coefficients of variation for total cholesterol, high-density lipoprotein-cholesterol, and triglycerides were 1.80, 1.23, and 3.93%, respectively.

C-reactive protein was measured using the high-sensitivity C-reactive protein (Hs-CRP) method on a Hitachi 911 analyzer with reagents from Denka Seiken (Tokyo, Japan) using previously validated techniques (24). Hs-CRP measurements were performed by a blinded core laboratory (Paul Ridker, M.D., Brigham and Women's Hospital, Boston, MA).

Postmenopausal status and PCOS determination

As previously published, postmenopausal status was classified, based on the presence of regular menses, time since the menses cessation, as well as FSH and LH measurements using a reproductive status algorithm (25). From this report, a woman classified as perimenopausal (defined as FSH 15–30 IU/liter and FSH > LH) was not included in the current analysis. All classifications of menopausal status were completed blinded to the coronary angiographic results.

Clinical features of PCOS included biochemical evidence of hyperandrogenemia [top quartile of androstenedione (≥701 pg/ml), testosterone (≥30.9 ng/dl), or free testosterone (≥4.5 pg/ml)] and history of irregular menses (n = 104). The use of an upper quartile, as a measure of high risk, was based on our attempt to limit those classified as at risk to only those with the most elevated androgen measurements. A pattern of irregular periods was defined as that occurring during a woman's premenopausal years, since menses onset, but did not include the time period when she was pregnant or taking birth control pills. Specifically, women were asked if, since menses onset, before menopause (excluding the perimenopausal years) they had periods that occurred on a monthly basis. Of the 104 women with clinical features of PCOS, a total of 20 reported a prior diagnosis of PCOS. Of this latter cohort of 20 women, 85% noted history of irregular menses, with 65 and 82% noting top quartile mea-surements in free testosterone and testosterone. This definition of clinical features PCOS conforms to the 1990 NIH criteria (26) and the more recent 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine criteria for PCOS (27).

Measurement of angiographic CAD

Quantitative analysis of coronary angiography was performed by an experienced core laboratory. Methods and design of the core laboratory have been previously published (28). Measurements included the presence, extent, and severity of obstructive, epicardial coronary artery stenoses. Significant CAD was defined as at least 50% luminal diameter stenosis in at least one epicardial coronary artery.

Follow-up procedures

Enrolled patients gave informed consent for participation in the follow-up portion of this study. Institutional review board approval was obtained for the follow-up methods described herein. The follow-up procedures included patient contacts at 6 wk after angiography and then yearly thereafter. Patients were contacted by experienced study coordinators who completed a scripted interview about major adverse CV events or hospitalizations. For patients no longer living, a primary relative was queried as to the cause of death or any related CV hospitalizations during the preceding follow-up time period.

The primary endpoint for this analysis was time to CV death or nonfatal myocardial infarction (MI). If a CV event was identified, the site investigator was contacted for confirmation of the date and its occurrence. When available, death certificates were used to discern cause of death. The cause of death was reviewed by two investigators blinded to the clinical and angiographic data. In the case of discrepant death classification, adjudication was accomplished using a third reviewer. CV death was defined as that resulting from sudden cardiac death, end-stage congestive heart failure, acute MI, peripheral arterial disease, or cerebrovascular accident. Follow-up was complete in more than 95% of surviving patients with prospective annual follow-up occurring through 6 yr.

Statistical analysis

The frequency of historical and other categorical risk factors was compared for women with and without clinical features of PCOS using a χ^2 statistic. Age and other continuous measures (*e.g.* laboratory measurements) were compared using ANOVA techniques. A general linear model was used to control for other confounding variables (*e.g.* angiographic CAD severity) when comparing continuous measures in women by their clinical features of PCOS status. For skewed data, log transformations were applied or categorical comparisons were performed using a χ^2 statistic.

We additionally evaluated the association between clinical features of PCOS and obstructive CAD, defined as at least 50% stenosis. Multivariable logistic regression model was used, with PCOS status as the primary independent variable, and included statistical adjustment for traditional cardiac risk factors (including hypertension) and the metabolic syndrome risk factors.

The primary endpoint of this study was to compare time to CV death or nonfatal MI (n = 55) for women with and without clinical features of PCOS. We performed a subset analysis of time to CV death as a lone endpoint (n = 25). A secondary analysis examined time to CV events including death or MI as well as cerebrovascular accidents (n = 68). Kaplan-Meier survival curves were calculated to estimate time to CV events. Univariable and multivariable Cox proportional hazards models were fit to estimate hazard ratios for women with and without clinical features of PCOS. From the univariable Cox model, a hazard ratio and 95% confidence interval (CI) were calculated. Given the 55 primary outcomes, model overfitting was avoided by limiting the number of variables included within a multivariable model. We *a priori* identified candidate variables for risk adjustment, including the metabolic syndrome criteria and traditional cardiac risk factors (*e.g.* hypertension) as well as angiographic CAD. Although a total of 54 women had bilateral oopherectomy, the inclusion of this variable in prognostic models did not change the results presented herein ($P > 0.7$ for this variable in our multivariable Cox model). Additionally, exclusion of these women also did not change the current results. Finally, a first-order interaction of PCOS status by Hs-CRP categories of below 1, 1 to less than 3, and 3 or greater mg/dl was also evaluated. Regression diagnostics were performed, including evaluation of patient outliers as well as evaluating criteria for the proportional hazards assumption.

Results

Correlative results of irregular menses with androgen measurements (Table 1)

In women with a self-reported history of irregular menses during adulthood before menopause (excluding pregnancy or while taking birth control pills), there was a greater frequency of top quartile measurements of androstenedione ($P = 0.006$) and free testosterone ($P = 0.05$).

Past medical history for women with PCOS (Tables 2 and 3)

The age of menopause was 52.3 yr for women with clinical features of PCOS compared with 54.3 yr for those without such characteristics ($P = 0.197$). The younger age of menopause largely had to do with a greater frequency of bilateral oopherectomy occurring more often in women with clinical features of PCOS (35.0 *vs.* 24.7% for non-PCOS women, $P = 0.052$). Of those undergoing bilateral oopherectomy, women with clinical features of PCOS reported a younger age of menopause (43.6 ± 14 yr) compared with 50.1 ± 10 yr for women without clinical features of PCOS ($P = 0.028$). A similar age of menopause was noted for remaining women (55.1 ± 9 to 56.0 ± 10 yr). Women with clinical features of PCOS were more often diabetic ($P = 0.022$) and obese ($P = 0.006$) and met criteria for the metabolic syndrome ($P = 0.001$). In addition, women with clinical features of PCOS were more often insulin resistant, as defined by a HOMA index of at least 2.5 (Table 3; $P < 0.0001$).

Average Hs-CRPs were higher for women with clinical features of PCOS [1.19 mg/dl (95% CI = 0.76–1.61)] compared with women without clinical features of PCOS [0.78 mg/dl (95% CI = 0.66–0.90), $P = 0.025$]; using a general linear model controlling for statin use, hypertension, low-density lipoprotein (LDL) cholesterol, smoking history, metabolic syndrome, and angiographic CAD (Fig. 1).

Relation to angiographic CAD

Women with clinical features of PCOS had more prevalent CAD, with multivessel disease being noted in 32% as compared with 25% of women without clinical features of PCOS (Table 2; $P = 0.044$). For the WISE women, age- and body

TABLE 1. Frequency of history of irregular menses by top quartile of androgen measurements

	Irregular menses (n = 104)	No irregular menses (n = 286)	*P* value
Androstenedione ≥ 701 pg/ml	20.2%	5.8%	0.006
Testosterone ≥ 30.9 ng/dl	45.5%	27.5%	0.19
Free testosterone ≥ 4.5 pg/ml	63.6%	34.8%	0.05
SHBG < 30.9 nmol/liter	81.8%	27.4%	<0.0001

TABLE 2. Clinical characteristics of women with and without clinical features of PCOS

	PCOS (n = 104)	No PCOS (n = 286)	*P* value
Age (yr)	62.5 ± 10	65.8 ± 9	0.003
Age at menopause (yr)	52.3 ± 13	54.3 ± 10	0.197
Bilateral surgical oopherectomy	35.0%	24.7%	0.052
History of depression requiring treatment	26.9%	17.2%	0.038
Current smoker	26.0%	15.8%	0.026
CAD extent			0.044
<50% stenosis	48.2%	58.3%	
1 vessel CAD	19.5%	16.5%	
2 vessel CAD	14.3%	11.7%	
3 vessel CAD	18.0%	13.5%	

Data represent percentage or mean ± SD. This result persisted in a general linear model controlling for prior hysterectomy and the patient age at hysterectomy.

mass index-adjusted PCOS status was associated with a 1.71-fold (95% CI = 1.09–2.83) increased odds of angiographic CAD (Table 4). PCOS status remained an independent estimator of angiographic CAD in a subsequent multivariable model that also included covariate adjustment for diabetes and triglyceride measurements ($P = 0.038$; Table 4). Of the biochemical markers, the strongest association to angiographic CAD was noted with free testosterone where 24.3% of women with top quartile scores had multivessel CAD, compared with 15.6% of those with lower values ($P = 0.037$).

TABLE 3. Laboratory measurements[a] and risk factors for the metabolic syndrome for women with and without clinical features of PCOS

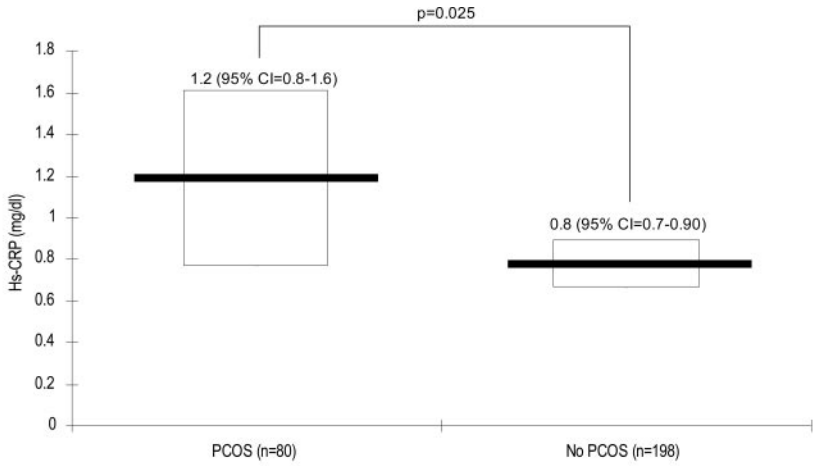
	PCOS (n = 104)	No PCOS (n = 286)	*P* value
Cardiac risk factors			
Hypertension	60.1%	44.2%	<0.0001
Diabetes mellitus	32.5%	24.4%	0.022
Dyslipidemia	64.2%	58.1%	0.29
Total cholesterol (mg/dl)	203.7 ± 49	194.4 ± 46	0.11
LDL cholesterol (mg/dl)	120.2 ± 41	114.4 ± 42	0.31[a]
HDL cholesterol (mg/dl)	50.8 ± 12	52.4 ± 11	0.26[a]
<50 mg/dl	54.8%	43.4%	0.044
Triglycerides (mg/dl)	184.3 ± 147	147.0 ± 113	<0.0001
>150 mg/dl	54.8%	36.3%	0.002
Body mass index (kg/m^2)	31.1 ± 7	28.4 ± 6	0.006
≥30 kg/m^2	50.0%	31.5%	0.016
Waist / hip ratio	0.885 ± 0.12	0.857 ± 0.11	0.040
Range	0.70–1.30	0.64–1.62	
Waist circumference (inches)	38.7 ± 7	36.9 ± 8	0.056
>35 inches	69.4%	60.0%	0.076
Blood pressure (mm Hg)			
Systolic	139.9 ± 20	140.1 ± 22	0.92
Diastolic	77.4 ± 10	75.7 ± 11	0.16
Age at hypertension diagnosis (mean ± SD in yr)	44.9 ± 14	52.0 ± 15	0.002
Fasting glucose (mg/dl)	132.1 ± 67	126.1 ± 58	0.42[b]
>110 mg/dl	45.3%	43.1%	0.72
Age at diabetes diagnosis (yr)	51.0 ± 14	53.3 ± 13	0.31
Insulin resistance[c]	33.7%	22.1%	0.001
Triglyceride/HDL ratio	3.9 ± 3.9	2.9 ± 2.5	<0.0001
>3.0	55.9%	38.7%	0.005
No. of metabolic syndrome risk factors (mean±SD)	2.9 ± 1.4	2.4 ± 1.3	0.014
0	7.1%	8.9%	0.001
1	13.6%	19.0%	
2	23.4%	28.6%	
≥3	55.8%	43.6%	

Data are presented as percentage or mean ± SD. The available sample size is: n = 328, n = 285, n = 330 for available HDL, LDL, and total cholesterol as well as n = 330 for triglycerides and n = 327 for glucose. HDL, High-density lipoprotein.

[a] These results persisted in a general linear model controlling for a history of dyslipidemia and statin use.

[b] These results persisted in a general linear model controlling for a history of diabetes.

[c] Insulin resistance was defined using a threshold of HOMA-IR ≥ 2.5 (17).



*p value was calculated using a general linear model controlling for statin use, LDL cholesterol, hypertension, metabolic syndrome, history of smoking, and angiographic coronary artery disease severity.

FIG. 1. Average Hs-CRP values (95% CI) for women with and without clinical features of PCOS. Hs-CRP data were available in 278 of the 390 postmenopausal women.

PCOS relationship to CV events

During follow-up, a total of 55 CV events (25 CV deaths) were documented with a cumulative Kaplan-Meier survival rate of 86.1%. For the androgen measurements, univariable models were of borderline significance and confounded by insulin resistance and obesity (univariable *P* range from 0.11 to 0.26). Crude event rates were approximately 29% higher for women in the top quartile of free testosterone compared with those in the lowest quartile; a similar pattern was noted with all androgen measurements. In a model including HOMA, history of diabetes, as well as waist circumference, predicted CV event rates that ranged from 8.0 to 15.1% across quartiles of free testosterone (Fig. 2; $P = 0.03$).

We next included a premenopausal history of irregular menses in the definition of PCOS along with biochemical evidence of hyperandrogenemia. Survival free from CV death was 90.4% for PCOS compared with 94.8% for non-PCOS women [hazard ratio = 2.1 (95% CI = 0.9–4.6), $P = 0.067$]. Cumulative Kaplan-Meier CV event-free survival (including CV death or nonfatal MI) was 78.9% for women with PCOS (n = 104) compared with 88.7% for women without PCOS (n = 286) and compared with 78.9% for those with clinical features of PCOS (Fig. 3; n = 104, $P = 0.006$). A significant difference in CV event-free survival was noted at 1 yr of follow-up ($P = 0.009$). In a univariable Cox model, women with clinical features of PCOS had a 3.3-fold (95% CI = 1.8–5.9) higher risk of CV death or MI ($P < 0.0001$). Similarly, women with clinical features of PCOS had reduced CV event-free survival, including stroke (69%), when compared with women without PCOS (88%) (hazard ratio = 2.3, 95% CI = 1.4–3.8, $P = 0.001$).

This relationship of worsening event-free survival for PCOS women was maintained in risk-adjusted models controlling for age, body mass index at least 30 kg/m^2, diabetes, and angiographic CAD (Table 5; adjusted hazard ratio = 1.6, $P = 0.002$).

In a model including Hs-CRP, PCOS status remained statistically significant (hazard ratio = 2.9, 95% CI = 1.5–5.6, $P = 0.001$). Furthermore, a first-order interaction term of PCOS status by Hs-CRP revealed that women with clinical features of PCOS and Hs-CRP at least 3.0 mg/dl had a 12.2-fold (95% CI = 4.3–35.0) higher risk of CV death or MI than women without PCOS ($P < 0.0001$).

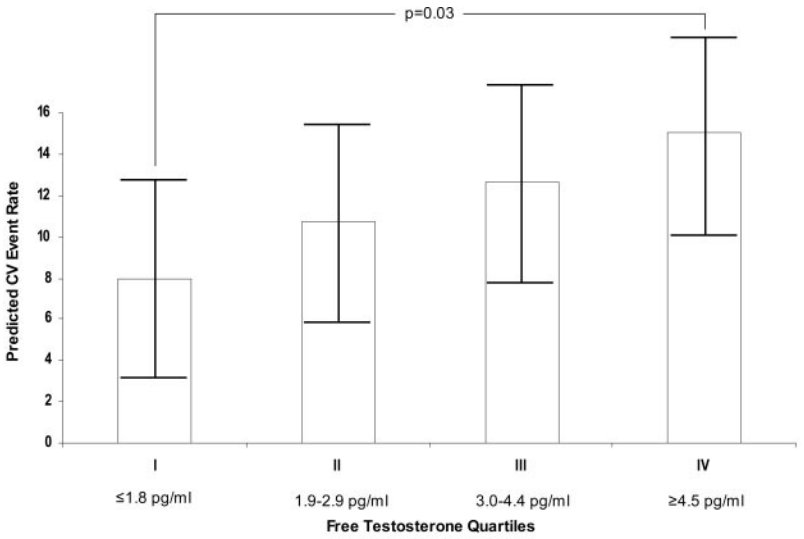
Discussion

Our findings demonstrate that historical definitions of PCOS combined with postmenopausal measurements of hyperandrogenemia may identify a cohort of women with more frequent angiographic CAD and an elevated risk of adverse CV events. These results support the concept that, in postmenopausal women, biochemical and clinical features of PCOS along with the associated cardiac risk factor clustering places females at heightened risk for CV disease (29–34). Prior reports have noted a higher frequency of subclinical atherosclerosis in PCOS women (11, 35–37), but reports focusing specifically on the prognostic utility of clinical features of PCOS in postmenopausal women have not been published (12–14, 38). Wild *et al.* (39) noted a higher prevalence of cerebrovascular disease, whereas other reports in largely premenopausal cohorts could not establish the link between PCOS and CV disease (12–14). These prior reports most often explored the link between PCOS and CV disease early in a woman's lifespan, with limited evaluations focusing on the postmenopausal years.

TABLE 4. Multivariable logistic regression model[a] estimating angiographically significant CAD, defined as a coronary stenosis ≥ 50%

	Odds ratio	95% CI	*P* value
Age- and body mass index-adjusted model			
Clinical features of PCOS	1.71	1.09–2.83	0.035
Multivariable model			
Clinical features of PCOS	1.88	1.06–3.40	0.038
Age (yr)	1.08	1.05–1.11	<0.0001
Diabetes	2.89	1.70–4.91	<0.0001
Body mass index ≥ 30 kg/m^2	1.52	1.09–2.11	0.013
Triglycerides ≥ 150 mg/dl	2.68	1.64–4.38	<0.0001

[a] All other candidate variables including common cardiac risk factors (*e.g.* current smoking) as well as Hs-CRP were removed from this model due to $P > 0.20$.



*Predicted CV Event Rate is based on a multivariable Cox model including HOMA, waist circumference, and a history of diabetes.

FIG. 2. Predicted CV event rates by quartile of free testosterone ranging from 8.0 to 15.1% for levels from no more than 1.8 to at least 4.5 pg/ml ($P = 0.03$).

The current study results provide one potential hypothesis that may be operating in hyperandrogenemic women (12–14). Prior studies have used relatively well-characterized premenopausal women with PCOS who have relatively low rates of CV disease in follow-up and have not controlled for diabetes (12–14). In a prior series, the standardized mortality ratio for circulatory disease was 0.83, suggesting 17% lower odds of death in women with PCOS; however, a failure to focus on women with more lengthy exposure to atherogenic risk factors may have contributed to these results (12). Additionally, examination of biochemical evidence of hyperandrogenemia alone was ineffective at identifying women with an elevated risk of ischemic heart disease death (38). However, in the current report, we hypothesize that the protracted influence and persistent manifestation of clinical features of PCOS may promote an accelerated likelihood of angiographic CAD as well as a higher risk of CV events only as exposure times lengthen substantially (*i.e.* postmenopausally). Moreover, it may be that the combination of hyperandrogenemia with a substantial cardiac risk factor burden and postmenopausal drop in endogenous estrogen provides the atherogenic milieu to increase cardiac risk. Although our definition of menstrual irregularities was derived from self-reported historical data, its addition to our elevated androgen measures further refined this characterization of "clinical features of PCOS," resulting in a high degree of predictive accuracy for CV events as well as a greater frequency of angiographic CAD. Prior reports have noted that the inclusion of menstrual irregularities, such as in the WISE, provided an improved link to CV events (14). The current results, using a well-characterized group of postmenopausal women, with rigorously measured risk factors that integrate both historical and biochemical features of PCOS as well as angiographic CAD and a sufficient length of follow-up time demonstrate an adverse independent association between clinical features of PCOS and CV outcomes.

A critical question is whether the heightened CV risk observed in the women with clinical features of PCOS as defined is due primarily to PCOS-related hyperandrogenism and/or to the associated risk factor clustering, including insulin resistance and the metabolic syndrome. We devised risk-adjusted predictive models, controlling for an array of traditional cardiac and metabolic syndrome risk factors as well as angiographic CAD severity. Our results suggest that postmenopausal women with clinical features of PCOS have an elevated risk of CV death or nonfatal MI that is independent of their underlying clinical risk, suggesting that PCOS-related protracted hyperandrogenism may be one mechanism responsible for their adverse cardiac risk. Further prospective work in women fully characterized for PCOS in the pre- to postmenopausal years is needed for confirmation.

More recent reports observed a greater frequency of risk markers for atherosclerosis, including more frequent endothelial dysfunction and a greater plaque burden for women with PCOS (11, 35–37, 40). In younger cohorts of PCOS women ages 30–45 yr, coronary artery calcification, a measure of subclinical atherosclerotic disease burden, was more prevalent in PCOS women (39%) than in matched controls (21%; odds ratio = 2.4; $P = 0.05$) or in community-dwelling women (9.9%; odds ratio = 5.9; $P < 0.001$) (11). In a related study, younger women with PCOS had significantly increased carotid intima-media thickness when compared with age- and body mass index- matched controls without PCOS ($P < 0.0001$) (40). Our results in older, postmenopausal women noted 2.5 higher odds of obstructive CAD for those with clinical features of PCOS, even when controlling for metabolic and common cardiac risk factors.

The current data also reveal that, similar to reports using atherosclerotic imaging, inflammatory markers are also more often elevated in women with clinical features of PCOS, even when controlling for the confounding effects of statin therapy use, hypertension, LDL cholesterol, smoking history, metabolic syndrome, and the severity of angiographic CAD ($P = 0.025$).

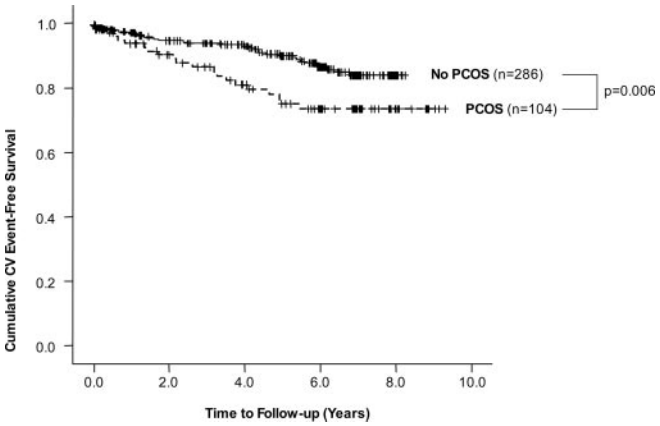


FIG. 3. Cumulative unadjusted CV death or MI free survival in postmenopausal women with or without clinical features of PCOS ($P = 0.006$).

TABLE 5. Multivariable Cox proportional hazards model estimating time to cardiovascular death or nonfatal MI

	Hazard ratio	95% CI	*P* value
Age- and body mass index-adjusted model			
Clinical features of PCOS	1.61	1.22–2.12	0.001
Multivariable model			
Clinical features of PCOS	1.59	1.19–2.12	0.002
Age (yr)	1.02	1.00–1.04	0.058
Diabetes	2.08	1.25–3.47	0.005
Body mass index $\geq$ 30 kg/m^2	1.01	0.66–1.55	0.97
Angiographic CAD	2.78	1.75–4.43	<0.0001

Moreover, women with clinical features of PCOS with elevated Hs-CRP had a 12.2-fold higher risk of CV death or nonfatal MI ($P < 0.0001$) than women without clinical features of PCOS and lower levels of Hs-CRP, suggesting that the independent adverse association between PCOS status and CV events after menopause may act vis-a-vis an inflammatory pathway.

Our women with clinical features of PCOS had a greater risk factor burden at a younger age, and it therefore could be hypothesized that this combination may promote longer exposure times for atherogenic risk factors and altered metabolic states, placing a woman at increased risk of CV disease (14, 33). It is likely that the use of hysterectomy at an early age for bleeding episodes in women with PCOS may also be contributory. In our cohort, women with clinical features of PCOS more often underwent bilateral surgical oopherectomy, largely at a younger age, contributing to the longer duration of exposure to atherogenic risk factors. Alternatively, women with clinical features of PCOS experiencing a CV event were significantly younger in our study. Therefore, it is likely that their greater burden of premenopausal subclinical disease, as noted previously (35–37, 40), coupled with metabolic dysfunction within an inflammatory milieu promotes more rapid progression of CAD from subclinical to clinical disease states. This is consistent with prior data noting that, as women age, the rate of carotid atherosclerotic disease progression is greater in women with PCOS compared with women without PCOS (40). This is also supported by our results noting early separation in CV event-free survival at 1 yr between postmenopausal women with and without clinical features of PCOS ($P = 0.009$).

Consistent with prior data, we did find a significantly higher prevalence of diabetes mellitus among our postmenopausal women with clinical features of PCOS (32, 41), but notably our results also demonstrate a strong association between PCOS status and CV events that is independent of diabetes. A recent meta-analysis noted a direct relationship between hyperandrogenic states and incident diabetes in women (42). This evidence synthesis reported approximately 20% higher risk of type 2 diabetes in women with higher testosterone and reduced SHBG levels. Indeed, these findings are consistent with prior epidemiological data demonstrating that diabetic premenopausal women have more frequent menstrual irregularities, lower blood estrogen levels, and higher androgen levels compared with nondiabetic women (14, 34, 43). These results suggest that women with PCOS are at heightened CV risk from both PCOS and the associated diabetes.

Study limitations

The current study results are limited by our lack of a more complete description of PCOS variables, such as hirsutism or polycystic ovaries. It should be noted that we identified women with clinical features of PCOS in their postmenopausal years that may or may not have been hyperandrogenemic premenopausally. Despite this, we believe that the notation of risk in this cohort with clinical features of PCOS may define an older at-risk group of women who may benefit from earlier CV risk evaluation. The prevalence of clinical features of PCOS is higher in this clinical cohort with more frequent metabolic syndrome, obesity, and diabetes when compared with prevalence rates from the general population (14, 34). The value of these phenotypic findings in postmenopausal women may, however, be less when compared with premenopausal women. These results are also potentially limited by confounding related to traditional risk factor clustering, although our analyses demonstrate independent adverse effects of PCOS status on CV disease outcomes. Future prospective work in women with established PCOS who transition to their postmenopausal state is needed.

Conclusions

Among postmenopausal women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia, clinical features consistent with PCOS are associated with greater angiographic CAD and adverse CV events. These findings suggest that identification of clinical features of PCOS, in postmenopausal women, may provide an opportunity for risk factor intervention for the prevention of CAD and CV events.

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