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Cardiovascular Disease and 10-Year Mortality in Postmenopausal Women with Clinical Features of Polycystic Ovary Syndrome

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Abstract

Background: Women with polycystic ovary syndrome (PCOS) have greater cardiac risk factor clustering but the link with mortality is incompletely described.
Objective: To evaluate outcomes in 295 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.
Materials and Methods: A total of 25/295 (8%) women had clinical features of PCOS defined by a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenemia, 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 estimated death ($n=80$).
Results: Women with clinical features of PCOS had an earlier menopause ($p=0.01$), were more often smokers ($p<0.04$), and trended toward more angiographic coronary artery disease (CAD) ($p=0.07$) than women without these features. Cumulative 10-year mortality was 28% for women with ($n=25$) versus 27% without clinical features of PCOS ($n=270$) ($p=0.85$). PCOS was not a significant predictor ($p=$NS) in prognostic models including diabetes, waist circumference, hypertension, and angiographic CAD.
Conclusion: From this longer-term follow up of a relatively small cohort of postmenopausal women with suspected ischemia, the prevalence of PCOS is similar to the general population, and clinical features of PCOS are not associated with CAD or mortality. These findings question whether identification of clinical features of PCOS in postmenopausal women who already have known cardiovascular disease provides any additional opportunity for risk factor intervention.

Introduction

Despite risk factor clustering, studies published to date have failed to demonstrate a uniform association between polycystic ovary syndrome (PCOS) and cardiovascular (CV) disease.[1–4] 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.

A prior published report from our group (Women's Ischemia Syndrome Evaluation [WISE]) was recently withdrawn due to coding errors discovered following a request of

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our data files for a large PCOS-CV disease meta-analysis.[5] The prior erroneously coded data analyses suggested that historical definitions of PCOS combined with postmenopausal measurements of hyperandrogenemia identified a cohort of women with higher rates of obstructive coronary artery disease (CAD) and adverse CV events in postmenopausal women,[5] however, the correctly coded data failed to reproduce these findings.

The WISE now has longer-term all-cause mortality follow-up. We retested the hypothesis that women with clinical features of PCOS more often had angiographic CAD and higher mortality in a carefully characterized group of postmenopausal women enrolled in the National Institutes of Health (NIH)–National Heart, Lung, and Blood Institute (NHLBI) sponsored WISE using the correctly coded dataset.

Materials and Methods

Subject 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 angiographically significant 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 923 WISE participants enrolled between 1997 and 2001[6] with complete demographic, reproductive status, and coronary angiographic data (549), 253 were currently using hormone replacement therapy (one missing information), and none were using oral contraceptives, leaving 295 (35%) were postmenopausal, nonhormone therapy and nonoral contraceptive users, who could be classified for clinical features of PCOS. Because the majority of CV disease occurs in postmenopausal women, we excluded pre- and perimenopausal women.

Baseline data collection

All WISE subjects 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.[7] More detailed information on the WISE study design has been published.[6] Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) index with a threshold of at least 2.5.[8]

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

Androstenedione and total testosterone were quantified in serum by previously described and validated RIAs.[9,10] 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, respectively.

Free testosterone concentration in a given sample was calculated using the measured total testosterone and sex hormone-binding globulin (SHBG) concentrations in the same sample and an assumed constant concentration of albumin.[11,12] The validity of the calculation method for determining free testosterone concentrations has been reported.[13]

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.[14] 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.[15] Hs-CRP measurements were performed by a blinded core laboratory (Paul Ridker, MD, 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, age, and follicular stimulating hormone, and leutinizing hormone, and estradiol measurements using the WISE reproductive status algorithm.[16] From this report, a woman classified as perimenopausal was not included in the current analysis. All classifications of menopausal status were completed blinded to the coronary angiographic and mortality results. The past medical history of PCOS was self-report.

Clinical features of PCOS included biochemical evidence of hyperandrogenemia [top quartile of androstenedione (≥701 pg/mL), or testosterone (≥30.9 ng/dL), or free testosterone (≥4.5 pg/mL) for the population] and history of irregular menses. 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 but before menopause (excluding the perimenopausal years), they had periods that occurred on a monthly basis. Our definition of clinical features PCOS conforms to the 1990 NIH criteria[17] and the more recent 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine criteria for PCOS.[18]

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.[19] 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 weeks 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 death certificate was obtained and/or a primary relative was queried as to the cause of death or any related CV hospitalizations during the preceding follow-up time period. We used the National Death Index (NDI) to determine mortality status for participants 4 years after the final follow-up date and obtained death certificates. This extended our median follow-up period for mortality from 5.9 to 9.3 years. The NDI is a centralized database of death records established by the National Center for Health Statistics and available to approved researchers. For study purposes, we matched participants to NDI records using Social Security numbers to confirm mortality status and mortality dates.

The primary endpoint for this analysis was 10-year all-cause mortality. We additionally assessed 10 year time to CV death or 6 year 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, otherwise we used narratives from relatives and hospital records. The cause of death was reviewed by two study investigators blinded to the clinical and angiographic data. In the case of discrepant death classification, adjudication was accomplished using a third independent 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. Limited follow-up information on nonfatal events was available in more than 95% of surviving patients with prospective annual follow-up occurring through 6 year, while 10-year mortality was conducted using a NDI search and was 100% complete.

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 *t*-tests. Highly skewed variables are presented as medians (interquartile ranges [IQR]) and were compared using nonparametric Kruskal–Wallis tests. The primary endpoints of this study were all-cause mortality ($n=80$) or CV death ($n=52$) for women with and without clinical features of PCOS. A secondary analysis examined time to CV events including death or MI ($n=62$) or death, MI, or cerebrovascular accidents ($n=73$). Kaplan–Meier survival curves were calculated to estimate time to events. Univariable and multivariate Cox proportional hazards models were fit to estimate hazard ratios with 95% confidence interval (CI) for women with clinical features of PCOS. Given the small number of women with PCOS ($n=25$) model over fitting 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 (*e.g.*, triglycerides) and traditional cardiac risk factors (*e.g.*, hypertension) and obstructive CAD.

Results

Of the 295 women in our sample, 52 (18%) noted history of irregular episodes of vaginal bleeding and another 144 (49%) had measurements in free testosterone and testosterone in the top quartile. Twenty-five women (8% of the total) were classified as having clinical signs of PCOS based on history of both irregular menses and hyperandrogenemia (androgen levels in the upper quartile). Among women with and without a self-reported history of irregular menses there were no statistical differences in the presence of hyperandrogenemia or top quartile measurements of androstenedione, testosterone, or free testosterone ($p=0.90$, 0.40, 0.83, and 0.55, respectively), nor were there differences in the mean androgen values. Of the 25 women with clinical features of PCOS, a total of 2 (8%) reported a prior diagnosis of PCOS as defined versus 15/266 (5.6%) in the remaining 266 (4 missing) ($p=0.65$).

Women with clinical features of PCOS had an earlier menopause ($p=0.01$), were more often smokers ($p<0.04$), and had a trend toward more angiographic CAD ($p=0.08$) compared to women without clinical features of PCOS (Table 1). In addition, women with clinical features of PCOS had a trend toward higher fasting glucose ($p=0.06$) (Table 2). Hs-CRP levels did not differ in women with and without clinical features of PCOS ($p=$NS, data not shown).

Relation to angiographic CAD

Women with clinical features of PCOS had a trend toward more prevalent CAD, with multi (two or three) vessel disease being noted in 42% as compared with 27% of women without clinical features of PCOS (Table 1; $p=0.07$ by χ^2).

Table 1. Clinical Characteristics of Women With and Without Clinical Features of Polycystic Ovary Syndrome

	PCOS (n = *25*)	*No PCOS* (n = *270*)	p
Age, years	62.6 ± 11.6	64.8 ± 9.6	0.28
Age at menopause, years	41.1 ± 10.4	46.2 ± 7.0	0.004
Bilateral salpingo-oophorectomy, %	41.7	26.2	0.15
History of depression requiring treatment, %	28.0	18.5	0.48
Current smoker, %	36.0	17.1	0.04
CAD extent, %			
<50% stenosis	56.0	51.1	0.43
1 vessel CAD	0.0	21.2	0.07
2 vessel CAD	20.8	13.6	
3 vessel CAD	20.8	12.9	

CAD, coronary artery disease; PCOS, polycystic ovary syndrome.

Table 2. Laboratory Measurements and Risk Factors for the Metabolic Syndrome for Women With and Without Clinical Features of Polycystic Ovary Syndrome

	PCOS (n = *25*)	*No PCOS* (n = *270*)	p
Cardiac risk factors, %			
Hypertension	48.0	63.3	0.29
Diabetes mellitus	24.0	32.2	0.66
Dyslipidemia	64.0	54.1	0.52
Total cholesterol, mg/dL	195.3 ± 36.6	197.8 ± 48.5	0.80
LDL cholesterol, mg/dL	110.1 ± 29.4	116.2 ± 42.0	0.57
HDL cholesterol, mg/dL	47.9 ± 10.3	52.5 ± 11.2	0.05
<50 mg/dL, %	64.0	42.4	0.06
Triglycerides, mg/dL	198.7 ± 136.5	148.7 ± 88.5	0.08
>150 mg/dL, %	52.0	42.4	0.40
Body mass index, kg/m^2	28.7 ± 5.9	30.0 ± 6.7	0.37
≥30 kg/m^2, %	36.0	40.6	0.83
Waist/hip ratio	0.89 ± 0.12	0.87 ± 0.12	0.58
Range	0.73–1.28	0.68–1.62	
Waist circumference, inches	38.5 ± 7.6	37.9 ± 7.2	0.70
>35 inches, %	68.0	60.2	0.52
Blood pressure, mmHg			
Systolic	141.4 ± 19.9	140.4 ± 21.6	0.84
Diastolic	75.4 ± 12.5	76.7 ± 10.9	0.62
Age at hypertension diagnosis, years, mean ± SD	47.5 ± 11.6	50.5 ± 15.0	0.51
Fasting glucose, mg/dL	109.78 ± 46.5	121.4 ± 60.5	0.45
>110 mg/dL, %	12.5	34.6	0.10
Age at diabetes diagnosis, years	58.4 ± 9.6	51.5 ± 12.8	0.24
Insulin resistance, HOMA	3.07 ± 5.02	5.35 ± 8.24	0.12
Fasting glucose >110 and triglycerides >150 mg/dL, %	20	18	0.81
Triglyceride/HDL ratio	4.7 ± 3.9	3.0 ± 2.0	0.05
>3.0, %	52.0	43.0	0.41
No. of metabolic syndrome risk factors, mean ± SD	2.1 ± 1.2	1.8 ± 1.1	0.22
0, %	12.0	10.7	0.16
1, %	20.0	31.9	
2, %	20.0	31.1	
≥3, %	48.0	26.3	

HOMA, homeostasis model assessment; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

PCOS relationship to all-cause and CV mortality

Over a median of 9.3 (IQR 8.4, 10.3) years of follow-up, a total of 80 women died (52 due to CV causes). Raw mortality rates were 28% for women with clinical features of PCOS ($n = 25$) versus 27% for women without clinical features of PCOS ($n = 270$) ($p = 0.849$) (Figure 1), and 20% versus 17% for CV deaths ($p = 0.74$), respectively. PCOS was not a significant predictor of all-cause and CV mortality rates (HR 1.03 [95% CI 0.57–1.86], $p = 0.93$, and HR 0.82 [95% CI 0.37–1.81], $p = 0.62$). This finding remained consistent in prognostic models including diabetes, waist circumference, hypertension, and angiographic CAD as covariates. Models substituting a premenopausal history of irregular menses and biochemical evidence of hyperandrogenemia in place of PCOS failed to predict mortality, even after adjusting for (log) Hs-CRP. A study power calculation for the mortality provided a power of 0.0551 assuming an alpha significance level of 0.05.

As a secondary outcome, we also evaluated combined CV events that included nonfatal CV events including MI and cerebrovascular events in addition to CV death. A total of 62 women, including 6 (24%) of women with PCOS and 56 (21%) in those without PCOS, had either MI or CV death, and a total of 73 women, including 6 (24%) with PCOS and 67 (25%) without PCOS had either MI, cerebrovascular event, or CV death. In all cases, PCOS was not a significant predictor of either combined outcome ($p = 0.51$ and $p = 0.85$, respectively).

We also performed a sensitivity analysis, to determine whether bilateral salpingo-oophorectomy (BSO) was a factor in a possible relationship between PCOS and outcomes. A total of 80 women had a history of BSO (26% in women without clinical features of PCOS versus 42% in those with clinical features of PCOS; $p = 0.10$). In models that included PCOS and BSO, BSO did not predict mortality and did not substantively alter the relationship between PCOS and mortality.

Of the 25 women with clinical features of PCOS, a total of 2 (8%) reported a prior clinical diagnosis of PCOS versus 15/266 (5.6%) in the remaining 266 (4 missing) ($p = 0.65$). The mortality rates for these 15 self-identified women did not differ from the others [all-cause death: 4/15 (27%) versus 68/251 (27%), $p = 0.97$; CV death: 1/15 (7%) versus 46/251 (18%), $p = 0.25$]. Finally, additional modeling in the whole WISE cohort relating history of irregular menstrual cycling, hyperandrogenism, or self-reported PCOS failed to predict mortality.

Discussion

Our findings demonstrate that historical definitions of PCOS combined with postmenopausal measurements of

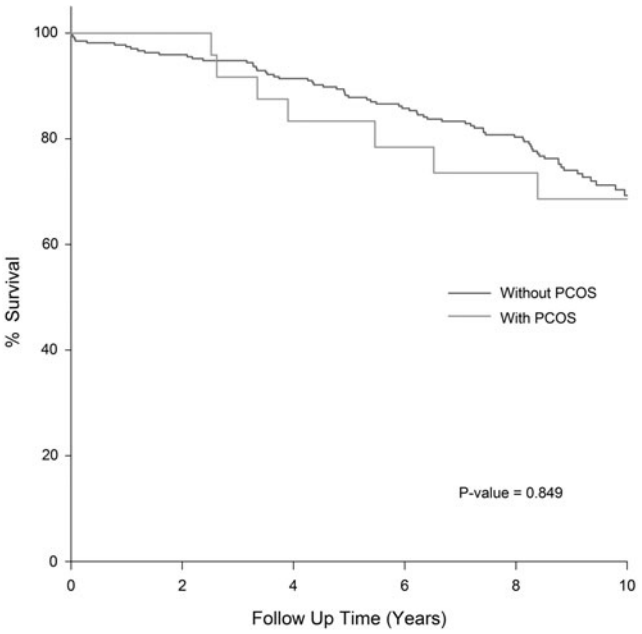

FIG. 1. Longer-term mortality by PCOS total $N = 295$, including 25 (8%) have clinical features of PCOS as defined, where 7 (28%) of the women with clinical features of PCOS died compared to 73 (27%) of the 270 without clinical features PCOS died. PCOS, polycystic ovary syndrome.

hyperandrogenemia does not identify women with higher longer-term all-cause mortality or adverse CV events despite a trend toward more frequent angiographic evidence of multivessel CAD. In addition, the prevalence of PCOS as defined among our women with suspected ischemia (8%) is not higher than that found in the general population in the United States.[20] Together, these results do not 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.[21–26] Prior reports have noted a higher frequency of subclinical atherosclerosis in PCOS women,[27–30] but reports focusing specifically on the prognostic utility of clinically defined PCOS in postmenopausal women have not been published.[1–3,31] Wild et al.[32] noted a higher prevalence of cerebrovascular disease, whereas other reports in largely premenopausal cohorts could not establish the link between PCOS and CV disease.[1–3] 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.

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 been controlled for diabetes.[1–3] In a prior series, the standardized mortality ratio for circulatory disease was 0.83, suggesting 17% lower odds of death in PCOS; however, a failure to focus on women with more lengthy exposure to atherogenic risk factors may have contributed to an association that links PCOS with lower mortality protective results.[3] Additionally, biochemical evidence of hyperandrogenemia alone did not identify women with an elevated risk of ischemic heart disease death.[31] The current report, with longer-term follow-up into the menopause supports these prior negative association findings.

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[27–30,33,34] and hospitalization.[35] In younger cohorts of PCOS women ages 30–45 years, 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; $p < 0.001$).[28] 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 ($p < 0.0001$).[33] Our results in older postmenopausal women noted only a trend toward a higher rate of obstructive CAD for those with clinical features of PCOS, which could be explained by survivor bias, whereby the younger PCOS women who had already died were not enrolled in our cohort.

Our women with clinical features of PCOS had an earlier onset of menopause and it therefore could be hypothesized that this could be placing a woman at increased risk of CV disease.[2,22] It is also possible that the use of hysterectomy at an early age for bleeding episodes in women with PCOS may also be contributory. While prior reports indicate a greater burden of premenopausal subclinical disease,[27,29,30,33] and a rate of carotid atherosclerotic disease progression that is greater in women with PCOS compared with women without PCOS,[33] we did not observe higher CV event or longer-term mortality rates in the menopause.

We did not find a significantly higher prevalence of diabetes mellitus among our postmenopausal women with clinical features of PCOS.[24,36] A recent meta-analysis noted a direct relationship between hyperandrogenic states and incident diabetes in women.[37] Women with higher testosterone and reduced SHBG levels had an approximate 20% higher risk of type 2 diabetes. Because prior epidemiological data demonstrate that diabetic premenopausal women have more frequent menstrual irregularities, lower blood estrogen levels, and higher androgen levels compared with nondiabetic women,[2,26,38] our current results that failed to find this suggest that postmenopausal identification of PCOS may be challenging.

Study limitations

This study is limited by our lack of a more complete description of PCOS variables, such as hirsutism or polycystic ovaries. Our cohort had a low prior medical history of PCOS, however self-reported PCOS (5.8%) is known to be lower than diagnosed PCOS (8.7%–17.8%).[39] We were not able to exclude secondary endocrinological conditions such as hypothyroidism or hypercortisolism. 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. The value of these phenotypic findings in postmenopausal women may be less when compared with premenopausal women. Specifically, our PCOS women were not substantially heavier than our non PCOS women. Both out PCOS and non-PCOS women had a relatively young age of menopause, potentially limiting out ability to detect group mortality difference. Because the control group does not truly reflect a normal, healthy

comparison group but is instead a population of women with substantial endocrine issues and higher risk of CAD, comparing women meeting PCOS criteria to this group cannot establish that PCOS is not associated with mortality in comparison to normal postmenopausal women. While adequate for statistical analyses, our relatively few ($n=25$) PCOS women is a limitation. We also have relatively limited study power ($p=0.055$) to detect a mortality difference, although the more frequent combined CV adverse event rate lack of difference argues somewhat against this. Prospective work in women with established PCOS who transition to their postmenopausal state in larger populations is needed.

Conclusions

Results from this long-term follow-up of a relative small cohort of postmenopausal women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia, clinical features consistent with PCOS are not associated with higher longer-term mortality or adverse CV events. These findings question whether identification of clinical features of PCOS in postmenopausal women provides an opportunity for risk factor intervention for the prevention of CAD and CV events.

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Author Disclosure Statement

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