



## Full Length Article

# Assessing the intersection of cardiovascular disease, venous thromboembolism, and polycystic ovary syndrome<sup>☆</sup>



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## ABSTRACT

**Introduction:** No study has examined how the relationship between polycystic ovary syndrome (PCOS) and atherosclerotic cardiovascular diseases (aCVD), of ischemic stroke (ISCH), acute myocardial infarction (AMI), and peripheral vascular disease (PAD), differ in the presence of venous thromboembolism (VTE).

**Materials and methods:** We performed a cross-sectional analysis using Truven Health Analytics MarketScan® Commercial databases from 2004–2011. The association between women aged 18–64 years with and without PCOS, and aCVD was assessed using VTE-stratified multivariable logistic regression models.

**Results:** Overall, women with PCOS were more likely to have aCVD, (aOR, 1.27; 95% CI, 1.10–1.46) especially ISCH (aOR, 1.56; 95% CI, 1.30–1.88), than women without PCOS. When stratified by VTE status, women with PCOS and a VTE diagnosis had a decreased odds of having any aCVD (aOR 0.67; 95% CI, 0.46–0.98), and VTE diagnosis more often preceded the occurrence of ISCH and AMI among women with PCOS compared with women without PCOS. **Conclusions:** Overall, women with PCOS were more likely to have aCVD, with stroke being the most prevalent manifestation. Although VTE often occurred before any aCVD, it appeared to have an inverse association with the development of ISCH, AMI, and PAD among women with PCOS, suggesting that aggressively treating VTE or aCVD early may limit the chances of developing the other thrombotic condition among women with PCOS.

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## 1. Introduction

Atherosclerosis is a chronic and progressive disease that develops early in life [1]. As atherosclerosis progresses, it can lead to the occurrence of cardiovascular events or atherosclerotic cardiovascular diseases (aCVD) the manifestations of which include acute myocardial infarction (AMI), ischemic stroke (ISCH), coronary heart disease, and peripheral vascular disease (PAD) [2,3].

From 2008–2010, the average rate of death attributable to all aCVD was 242.4 per 100,000 [4]. Thus, more than 2200 Americans died of aCVD each day, an average of 1 death every 39 seconds. Similarly, mortality data from 2010 indicated that stroke accounted for approximately 1 of every 19 deaths in the U.S. [4]

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age [5,6]. Its exact etiology is unknown, but it is characterized by a heterogeneous presentation of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. PCOS has been associated with increased risk for hypertension and metabolic abnormalities (e.g. low levels of high-density lipoprotein cholesterol) [7–10] and women with irregular menses also have manifestations of atherosclerosis, specifically AMI and ISCH, at younger ages [11]. Detection of traditional aCVD risk factors and surrogate markers of atherosclerosis at a young age in women with PCOS puts them at an increased risk for development of symptomatic aCVD [7,10,12].

Studies have likewise shown an association between venous thromboembolism (VTE) and atherosclerosis [13,14]. For example, Prandoni et al. 2003, demonstrated a relationship between asymptomatic atherosclerotic lesions and spontaneous venous thrombosis of the legs [13].

These findings are relevant to women with PCOS because Okoroh et al. 2012 found a higher prevalence of VTE among women with PCOS when compared with the general population [15]. One could infer that women with PCOS and VTE would be at the greatest risk of developing the sequelae of atherosclerosis compared with women

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**Table 1**  
Characteristics of women with and without polycystic ovary syndrome.

Factors	PCOS		No PCOS		P-value
	N = 125,268	%	N = 250,536	%	
<i>Age categories (years)</i>					
18–24	22,218	17.7	44,434	17.7	1.0
25–34	49,462	39.5	98,924	39.5	
35–44	36,523	29.2	73,048	29.2	
45–54	15,532	12.4	31,064	12.4	
55–64	1,533	1.2	3,066	1.2	
<i>Comorbidities</i>					
Metabolic syndrome	1,365	1.1	324	0.1	<.0001
Obesity	9,688	7.7	5,582	2.2	<.0001
Delivery	28,682	22.9	20,861	8.3	<.0001
Diabetes	5,739	4.6	4,762	1.9	<.0001
Hypertension	14,693	11.7	12,588	5.0	<.0001
Thrombophilia	451	0.4	242	0.1	<.0001
Infertility	4,526	3.6	1,299	0.5	<.0001
VTE	1,224	1.0	831	0.33	<.0001

PCOS, polycystic ovary syndrome; VTE, venous thromboembolism.

without PCOS and with VTE. Thus, the primary aim of this study was to determine how the association between PCOS and aCVD differs in the presence of VTE.

## 2. Material and methods

### 2.1. Data source

The data were derived from the 2004–2011 Truven Health Analytics MarketScan® Commercial databases which are longitudinal, de-identified health insurance claims data from large employers and health plans across the U.S. This commercial database has met or exceeded requirements of the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. The MarketScan databases are de-identified and meet the criteria for a limited-use dataset and does not require specific patient consent for participation in the study [16].

### 2.2. Study population

Women with PCOS were defined by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for clinical hyperandrogenism (acne (706.0 or 706.1), alopecia (704.0x), and/or hirsutism (704.1)), ovulatory dysfunction (626.0, 626.1, 626.2, 626.3, 626.4, 626.5, 626.6, 626.7, 626.8, or 626.9), and/or polycystic ovaries (256.4). To reduce misclassification of PCOS cases, we excluded women who met the criteria for PCOS and one or more related conditions: adrenal hyperplasia (255.0 or 255.9), hyperprolactinemia (253.1), or thyroid disorder (244.0, 244.1, 244.2, 244.3, 244.8, 244.9, 242.90, or 242.91). Due to the heterogenic nature of PCOS and its complex presentation and definition, we also looked for the presence of associated conditions seen among women with PCOS (such as obesity [278.0, 278.00–278.02, 783.1, or V77.8]; infertility [628.0 or 628.9]; syndrome X, or metabolic syndrome, [277.7]; hypertension [401.x, 405.x]; thrombophilia [289.81]; and diabetes [250.x]). Diagnoses reported on inpatient claims were considered valid; those based solely on outpatient claims required that the diagnoses be reported on two or more claims that occurred more than 30 days apart.

VTE during the study period was identified using ICD-9-CM codes for DVT (671.3x, 671.4x, 671.5x, 671.9x, 451.11, 451.19, 451.2, 451.81, 451.9, 453.1, 453.2, 453.40–453.42, 453.8, or 453.9), or PE (673.2x, 673.8x, 415.11, or 415.19), or both, on any inpatient or outpatient claim. We restricted outpatient diagnoses to those who had a filled prescription for an anticoagulant medication within 90 days of the diagnosis; for an inpatient diagnosis, only one ICD-9-CM code for DVT or PE was required.

CVD were defined by the presence of ICD-9-CM codes for ISCH (434.xx; 437.0, 437.1, 437.9; 438.x, and V12.54), AMI (410.xx, excluding 410.x2, which is used to designate follow up to the initial episode) or PAD (443.9).

A unique identifier was used to track women longitudinally over the study period. We included women enrolled for at least 12 months prior to and after the first PCOS diagnosis. The first report of PCOS diagnosis was considered the index date. Those who died during the 12 months after the PCOS diagnosis were also included since the post-index date enrollment restriction would not apply. Women who were not continuously enrolled  $\geq 12$  months prior to the index date or  $\geq 12$  months following the index date were excluded. Each woman with PCOS was exactly matched with two non-PCOS controls based on age at first PCOS diagnosis for the cases and age at first enrollment for the controls. Controls had to be enrolled for at least 12 continuous months. Cases and controls were restricted to women 18–64 years of age.

### 2.3. Data analysis

Bivariate analyses with two-tailed chi-square tests were used to compare the distribution of demographic and comorbid factors for women with and without PCOS. Fisher's exact P-values were used to compare the distribution of aCVD between women with and without PCOS. Conditional logistic regression on age was used to assess the likelihood of aCVD diagnosis (ISCH, AMI and PAD) among women with and without PCOS. We stratified the analysis by the presence or absence of a VTE diagnosis. PCOS was diagnosed among the study population before VTE or aCVD was diagnosed. The final models included only those factors that were statistically significant at a priori significance level ( $P < .05$ ) (obesity, diabetes, hypertension, and thrombophilia). All data were analyzed and managed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

The mean age of the study population was 33.4 years. Overall, there were 33 in-hospital deaths among women with PCOS and 99 among the controls. Women with PCOS had significantly higher proportions of all chronic comorbid conditions as well as thrombophilia, infertility, and VTE (Table 1). Of the 1224 women with PCOS and VTE, 529 (43.2%) had a PE. Of the 831 women without PCOS but with VTE, 310 (37.3%) had a PE. Overall, 839 (40.8%) of the study population with VTE had a PE.

Overall, women with PCOS were more likely to have aCVD, (aOR, 1.27; 95% CI, 1.10–1.46) especially ISCH (aOR, 1.56; 95% CI, 1.30–1.88), than women without PCOS. Stratification by VTE is shown in Table 2. Among women with PCOS and VTE, the unadjusted (OR, 0.72; 95% CI,

**Table 2**  
Association between PCOS, no PCOS and aCVD, by VTE status.

Variables	PCOS		No PCOS		OR	95% CI	aOR <sup>a</sup>	95% CI
	N	%	N	%				
<i>VTE = yes</i>								
Any aCVD	68	5.56	60	7.22	0.72	0.50–1.04	0.67	0.46–0.98
ISCH	35	2.86	31	3.73	0.73	0.44–1.21	0.66	0.38–1.70
AMI	15	1.81	8	0.65	0.34	0.14–0.81	0.35	0.14–0.87
PAD	28	2.29	18	2.17	1.04	0.57–1.92	1.03	0.56–1.90
<i>VTE = no</i>								
Any aCVD	372	0.30	372	0.15 <sup>b</sup>	2.02	1.75–2.34	1.28	1.11–1.49
ISCH	233	0.19	187	0.07 <sup>b</sup>	2.52	2.08–3.05	1.63	1.23–2.13
AMI	122	0.10	153	0.06 <sup>b</sup>	1.61	1.29–2.04	1.02	0.80–1.31
PAD	28	0.02	48	0.02	1.18	0.74–1.88	0.65	0.40–1.05

PCOS, polycystic ovary syndrome; aCVD, atherosclerotic cardiovascular diseases; VTE, venous thromboembolism; ISCH, ischemic stroke; AMI, acute myocardial infarction; PAD, peripheral vascular disease.

<sup>a</sup> All models adjusted for obesity, diabetes, hypertension, and history of thrombophilia.

<sup>b</sup> P value < 0.01.

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