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# Differences in coronary angiographic findings and outcomes between men and postmenopausal women with stable chest pain

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***Background*** **Despite the significant increase in cardiovascular events in women after menopause, studies comparing postmenopausal women and men are scarce.**

***Methods*** **We analyzed data from a nationwide, multicenter, prospective registry and enrolled 2412 patients with stable chest pain who underwent elective coronary angiography. Binary coronary artery disease (b-CAD) was defined as the ≥50% stenosis of epicardial coronary arteries, including the left main coronary artery.**

***Results*** **Compared with the men, postmenopausal women were older (66.6 ± 8.5 vs. 59.5 ± 11.4 years) and had higher high-density lipoprotein cholesterol levels (49.0 ± 12.8 vs. 43.6 ± 11.6 mg/dl, $P < 0.01$). The prevalence of diabetes did not differ significantly ($P = 0.40$), and smoking was more common in men than in postmenopausal women ($P \leq 0.01$). At enrollment, b-CAD and revascularization were more common in men than in postmenopausal women (50.3% vs. 41.0% and 14.4% vs. 9.7%, respectively; both $P < 0.01$). However, multivariate analyses revealed that revascularization [odds ratio (OR): 0.72; 95% confidence interval (CI): 0.49–1.08] was not significantly related to sex and a similar result was found in age propensity-matched population (OR: 0.80; 95% CI: 0.52–1.24). During the follow-up period, the secondary composite cardiovascular outcomes were lower in postmenopausal women than in men (OR: 0.55; 95% CI: 0.31–0.98), also consistent with the result using the age propensity-mated population (OR: 0.33; 95% CI: 0.13–0.85).**

***Conclusion*** **Postmenopausal women experienced coronary revascularization comparable to those in men at enrollment, despite the average age of postmenopausal women was 7 years older than that of men. Postmenopausal women exhibit better clinical outcomes than those of men if optimal treatment is provided. *Coron Artery Dis* 35: 314–321 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.**

**Coronary Artery Disease** 2024, **35**:314–321

**Keywords: chest pain, coronary artery disease, gender bias, percutaneous coronary intervention, postmenopause, stable angina**

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**Received** 27 December 2023 **Accepted** 6 January 2024.

## Introduction

Cardiovascular disease (CVD) is a major global health problem and is associated with mortality for both men and women [1]. Male sex is a risk factor for CVD; thus, studies on CVD have mainly included men [2]. However, women are not immune to ischemic heart disease, which is a contributing factor to significant CVD mortality [3–6]. Men and women exhibit differences in the manifestation, characteristics, pathogenesis and prognosis of CVD diseases [7,8]. Nevertheless, current guidelines do not provide sufficient sex-specific information [2,4,9]. The topic of CVD in women has attracted increasing attention, and related studies have increased recently [1]. However, this field still remains an 'under-researched area [4,7]'.

Women experience sex hormone changes throughout their lifetimes, and these changes are important factors in understanding the nature of heart disease and cardiovascular risk in women [3]. Women aged 18–39 years who do not have a risk profile have a low rate of developing long-term CVD and have low all-cause mortality [10]. When women experience menopause, the prevalence of cardiovascular risk factors such as central obesity, elevated blood sugar and dyslipidemia

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increases markedly [11]. Estrogen affects blood pressure (BP), endothelial cell function and heart remodeling. Changes in estrogen levels affect the immune system, which is related to vascular function, and can increase central obesity by changing body composition [12,13]. Menopause increases the risk of CVD and can cause an increase in BP [3,14]. Therefore, mortality from CVD is significantly low in young women but increases sharply with advancing age compared with that in men [15]. Women have been reported to experience their first acute myocardial infarction 9 years later than men did [16].

Owing to the heterogeneity of CVD between young and postmenopausal women, there are limitations when conducting studies involving all adult women in the same population. In the current study, we compared postmenopausal women and men with stable chest pain who visited an outpatient clinic and underwent elective invasive coronary angiography (CAG). We aimed to evaluate the characteristics and clinical outcomes of CVD in postmenopausal women.

## Materials and methods

### Data source and study population

This study was conducted using data from the Korean Women's Chest Pain Registry (KoROSE) registered from February 2011 to December 2020. The KoROSE, which is a nationwide, multicenter, prospective study, enrolled patients aged over 20 years who visited an outpatient clinic with stable chest pain, underwent invasive CAG to rule out coronary artery disease, and were followed up for approximately 3 years. Women were eligible for the registry if they (1) suspected coronary artery disease with 'stable' anginal symptoms with or without dyspnea [17], (2) suspected coronary artery disease at health screening, (3) had no significant structural or valvular heart disease and (4) had no prior myocardial infarction [18]. The registry also enrolled men from February 2014 for the comparison. The details of the registry have been published elsewhere [19–21].

Baseline data, including patient demographic and clinical characteristics, were obtained at the time of the index invasive CAG. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared, and obesity was defined as BMI ≥ 25 kg/m$^2$ [22]. Central obesity was defined as waist circumference ≥90 cm for men and ≥85 cm for women [23].

Hypertension was defined as a previous diagnosis of hypertension, use of antihypertensive drugs or BP ≥ 140/90 in repeated measurements. Diabetes mellitus (DM) was defined as a previous diagnosis of the disease by a physician, use of hypoglycemic agents or fasting blood glucose level ≥ 126 mg/dl in repeated tests. Dyslipidemia was defined as a previous diagnosis of dyslipidemia by a physician, use of antidyslipidemic medicines or low-density lipoprotein (LDL) cholesterol ≥160 mg/dl.

Early menopause was defined as menopause occurring at the age of ≤45 years in women. Women aged 60 years at the time of enrollment were considered to have menopause unless otherwise documented.

### Noninvasive cardiac evaluations

The treadmill test was performed according to the instructions of the attending physician if there was no contraindication, and the Bruce or modified Bruce protocol was used according to the standard protocol of each institution [24]. Positive results were defined as ≥1 mm horizontal ST depression, down-sloping ST depression or ST elevation from the J point during the exercise or recovery phase [25]. Transthoracic echocardiography was performed before or after index CAG. Transthoracic echocardiographic parameters were obtained according to the current recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging; the detailed measurements have been published elsewhere [26,27].

### Invasive procedures

CAG was performed according to the current guidelines [2]. Binary coronary artery disease (b-CAD) was defined as the ≥50% stenosis of epicardial coronary arteries, including the left main coronary artery. The binary stenosis of any epicardial coronary artery is regarded a coronary artery obstructive disease and is classified as a one-, two- or three-vessel disease according to the extent of the disease. For the diagnosis of vasospastic angina, a coronary provocation test was performed using ergonovine or acetylcholine according to the standard protocol of each institution. If luminal narrowing occurred in ≥90% of the cases after drug administration and was reversed after the intracoronary administration of nitroglycerin, the doctor judged it as positive [28].

Percutaneous coronary intervention (PCI) was conducted according to the instructions of the responsible physician and interventional cardiologist. All patients who underwent PCI received standard dual antiplatelet therapy, and unfractionated heparin was administered to maintain an activated clotting time of >250 s during the procedure. After the procedure, dual antiplatelet therapy was maintained according to the guidelines [2,9,29].

### Clinical outcomes

The primary outcome was the presence of b-CAD at the baseline CAG with or without revascularization of the lesion at the time of patient enrollment.

Secondary outcomes were defined as the presence of secondary composite cardiovascular outcomes during the

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follow-up period, including admission due to acute coronary syndrome, coronary revascularization, heart failure or stroke. Death was defined as death due to any cause.

### Statistical analysis

Categorical values are described as frequencies (%) by using the chi-square test. Continuous values were expressed as mean ± SD by using Student's *t*-test. If continuous values did not follow a normal distribution, the Mann–Whitney *U* test was performed and continuous variables were expressed as median and interquartile range [first quartile (Q1), third quartile (Q3)].

Univariate logistic regression models were first applied to each variable to assess the risk factors for the primary and secondary outcomes. Multivariable logistic regression was used to evaluate the independent risk of primary and secondary outcomes after adjusting for covariates. These covariates were statistically significant risk factors in the univariate analyses. If overlapping risk factors, such as elevated systolic BP, use of antihypertensive drugs and hypertension, were found to be significant in the univariate analysis, one representative covariate, such as hypertension, was used in the multivariate analysis.

For propensity-matched analysis, 1 : 1 greedy nearest neighbor propensity score matching method was used with precise matching control for age. Other covariates: high-density lipoprotein (HDL) cholesterol, DM, hypertension, smoking, statin, aspirin and regional wall motion abnormality (RWMA) were used for propensity matching variables. Standard mean difference was used for evaluation of matching balance. Another multivariable logistic regression was performed to evaluate the independent risk of primary and secondary outcomes using propensity-matched population.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, North Carolina, USA).

### Ethics statement

Each center participating in the KoROSE obtained approval from the institutional review board of each institution, and study subjects were enrolled after written informed consent was obtained from the registry. This study was approved by the institutional review board of our institution (approval no. ECT 12-8-1).

## Results

### Baseline demographics

This study included 901 men (37.4%) and 1511 postmenopausal women (62.6%). Table 1 presents the baseline clinical characteristics of the patients. Postmenopausal women were older than men (66.6 ± 8.5 vs. 59.5 ± 11.4, $P < 0.001$). Obesity (BMI ≥ 25 kg/m$^2$) was more common in men than in postmenopausal women ($P = 0.006$), but the prevalence of central obesity was similar in both groups ($P = 0.339$). Men were more likely to be current smokers than postmenopausal women were (35.5% vs. 3.2%, $P < 0.001$).

**Table 1 Baseline demographics and clinical characteristics**

| Characteristic | Male ($n = 901$) | Menopause female ($n = 1511$) | *P* value |
|---|---|---|---|
| Age | 59.5 ± 11.4 | 66.6 ± 8.5 | <0.001 |
| BMI, kg/m$^2$ | 25.2 ± 3.2 | 25.1 ± 3.5 | 0.427 |
| Obesity (BMI ≥ 25 kg/m$^2$) | 440 (51.6%) | 666 (45.7%) | 0.006 |
| Waist circumference, cm | 87.2 ± 8.0 | 82.7 ± 8.8 | <0.001 |
| Central obesity, %[a] | 164 (35.5%) | 332 (38.2%) | 0.339 |
| Smoking | | | |
| Never | 332 (40.8%) | 1309 (94.9%) | <0.001 |
| Current | 289 (35.5%) | 44 (3.2%) | |
| Former | 193 (23.7%) | 26 (1.9%) | |
| Early menopause | | 134 (8.9%) | |
| Systolic blood pressure, mmHg | 128.4 ± 17.3 | 126.9 ± 18.8 | 0.090 |
| Diastolic blood pressure, mmHg | 79.0 ± 11.7 | 75.6 ± 11.5 | <0.001 |
| Heart rate, per minute | 74.9 ± 13.7 | 74.0 ± 12.5 | 0.189 |
| Laboratory measurements | | | |
| Hemoglobin, g/dl | 14.4 ± 1.6 | 12.7 ± 1.4 | <0.001 |
| Glycated hemoglobin, % | 5.9 (5.5–6.7) | 6 (5.6–6.8) | 0.086 |
| Total cholesterol, mg/dl | 164.5 ± 41.7 | 172.4 ± 43.6 | <0.001 |
| HDL cholesterol, mg/dl | 43.6 ± 11.6 | 49.0 ± 12.8 | <0.001 |
| LDL cholesterol, mg/dl | 101.4 ± 36.5 | 102.3 ± 34.8 | 0.562 |
| Triglycerides, mg/dl | 124 (89–184) | 108 (79–149) | <0.001 |
| Creatinine, serum | 1.0 (0.9–1.1) | 0.7 (0.6–0.9) | <0.001 |
| Comorbidity, % | | | |
| Diabetes | 220 (27.4%) | 360 (25.7%) | 0.397 |
| Hypertension | 445 (53.3%) | 851 (59.4%) | 0.004 |
| Dyslipidemia | 172 (25.2%) | 347 (26.1%) | 0.639 |
| Concomitant medications, % | | | |
| Hypoglycemic agents | 186 (23.9%) | 309 (22.8%) | 0.567 |
| Statin | 397 (52.0%) | 747 (56.9%) | 0.029 |
| Thyroid drugs | 9 (1.2%) | 83 (6.4%) | <0.001 |
| Aspirin | 340 (44.8%) | 612 (48.3%) | 0.126 |
| Clopidogrel | 201 (26.7%) | 374 (29.9%) | 0.115 |
| Beta-blocker | 178 (23.5%) | 381 (30.4%) | 0.001 |
| ARB/ACEI | 254 (33.6%) | 457 (36.4%) | 0.205 |

Data presented as *N* (%), average ± SD or median (Q1, Q3).
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index.
[a]Central obesity is defined as waist circumference ≥90 cm for men and ≥85 cm for women.

Postmenopausal women had higher levels of total cholesterol (172.4 ± 43.6 vs. 164.5 ± 41.7 mg/dl, $P < 0.001$) and HDL cholesterol (49.0 ± 12.8 vs. 43.6 ± 11.6 mg/dl, $P < 0.001$) than those in men. Both groups had similar LDL cholesterol levels (102.3 ± 34.8 vs. 101.4 ± 36.5, $P = 0.562$). Men had higher triglyceride levels than postmenopausal women did ($P < 0.001$).

Postmenopausal women had a higher prevalence of hypertension (59.4% vs. 53.3%, $P = 0.004$) and higher usage of statins, beta-blockers and antithyroid drugs than men did (Table 1).

### Cardiac evaluations and coronary studies

More men than postmenopausal women underwent the treadmill test for chest pain evaluation, and men showed more positive results than those of postmenopausal women (24.9% vs. 18.6%, $P = 0.005$; Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/MCA/A649*). The left ventricular systolic function was similar in both groups ($P = 0.082$; Supplementary

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Table 2, Supplemental digital content 1, *http://links.lww.com/MCA/A649*). Postmenopausal women had a higher left ventricular mass (LVM) index and e/e' ratio than those exhibited by men (both, $P < 0.001$). However, more men had more RWMAs than postmenopausal women did (16.9% vs. 10.9%, $P < 0.001$), with no difference in the territory of RWMAs between the groups (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/MCA/A649*).

Men had a higher prevalence of b-CAD than postmenopausal women did, thus showing the overall higher frequency of stenosis and distribution of each vessel (Table 2). Myocardial bridging was more frequently observed in men than in postmenopausal women ($P = 0.008$). A total of 130 men (14.4%) and 147 postmenopausal women (9.7%, including 2 bypass surgeries) underwent revascularization after the index CAG ($P = 0.001$).

Figure 1 shows the difference and distribution of diagnoses between men and postmenopausal women at the time of the index CAG ($P < 0.001$). Angina pectoris, which is represented by the outer circle in Fig. 1, was the most common symptom in both groups (men: $n = 775$, 86%; postmenopausal women: $n = 1008$, 67%). The angina pectoris was subclassified and represented in the inner circle in terms of frequency: (atherosclerotic, obstructive) angina, microvascular angina, vasospastic angina and myocardial bridge for both groups.

Although the study candidates visited outpatient clinics for stable chest pain, some had myocardial infarction, which was more common in postmenopausal women than in men (postmenopausal women: $n = 183$, 12.1%; men: $n = 36$, 4.0%). Some patients had cardiac problems other than angina pectoris or myocardial infarction (postmenopausal women: $n = 45$, 3.0%; men: $n = 13$, 1.4%), including arrhythmia, cardiomyopathy, heart failure, pericarditis and primary pulmonary hypertension. More postmenopausal women ($n = 275$, 18.2%) than men ($n = 77$, 8.5%) were diagnosed with noncardiac diseases, such as gastrointestinal, musculoskeletal and psychological problems.

### Primary outcomes: binary coronary artery disease and revascularization

Univariate analyses (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/MCA/A649*) showed that sex, age, glycated hemoglobin, HDL cholesterol, DM, current smoking, use of antiplatelet agents, use of hypoglycemic agents, LVM and RWMA were associated with b-CAD and revascularization. Systolic BP, hypertension, use of beta-blockers and use of angiotensin receptor blockers were associated with b-CAD (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/MCA/A649*).

**Table 2 Coronary angiographic findings and revascularization**

| Characteristic | Male ($n = 901$) | Menopause female ($n = 1511$) | *P* value |
|---|---|---|---|
| Binary stenosis of major epicardial arteries | | | |
| Numbers of the stenosis | | | |
| ′0 | 447 (49.6%) | 893 (59.1%) | <0.001 |
| ′1 | 220 (24.4%) | 344 (22.8%) | |
| ′2 | 138 (15.3%) | 184 (12.2%) | |
| ′3 | 96 (10.7%) | 90 (6.0%) | |
| Locations of the stenosis | | | |
| LMCA | 34 (3.8%) | 19 (1.3%) | <0.001 |
| LAD | 352 (39.1%) | 467 (30.9%) | <0.001 |
| LCX | 192 (21.3%) | 256 (16.9%) | 0.008 |
| RCA | 232 (25.7%) | 253 (16.7%) | <0.001 |
| Revascularization | | | |
| PCI | 130 (14.4%) | 146 (9.7%) | <0.001 |
| CABG | 0 (0.0%) | 3 (75.0%) | 0.171 |
| PCI + CABG | 130 (14.4%) | 147 (9.7%) | 0.001 |
| Provocation test | | | |
| Yes | 235 (26.1%) | 439 (29.1%) | 0.116 |
| Positive result[a] | 130 (57.0%) | 189 (43.7%) | 0.001 |
| Other findings | | | |
| Myocardial bridging | 61 (9.2%) | 63 (5.8%) | 0.008 |

CABG, coronary artery bypass graft surgery; LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.
[a]Those who showed positive result among those who underwent provocation tests.

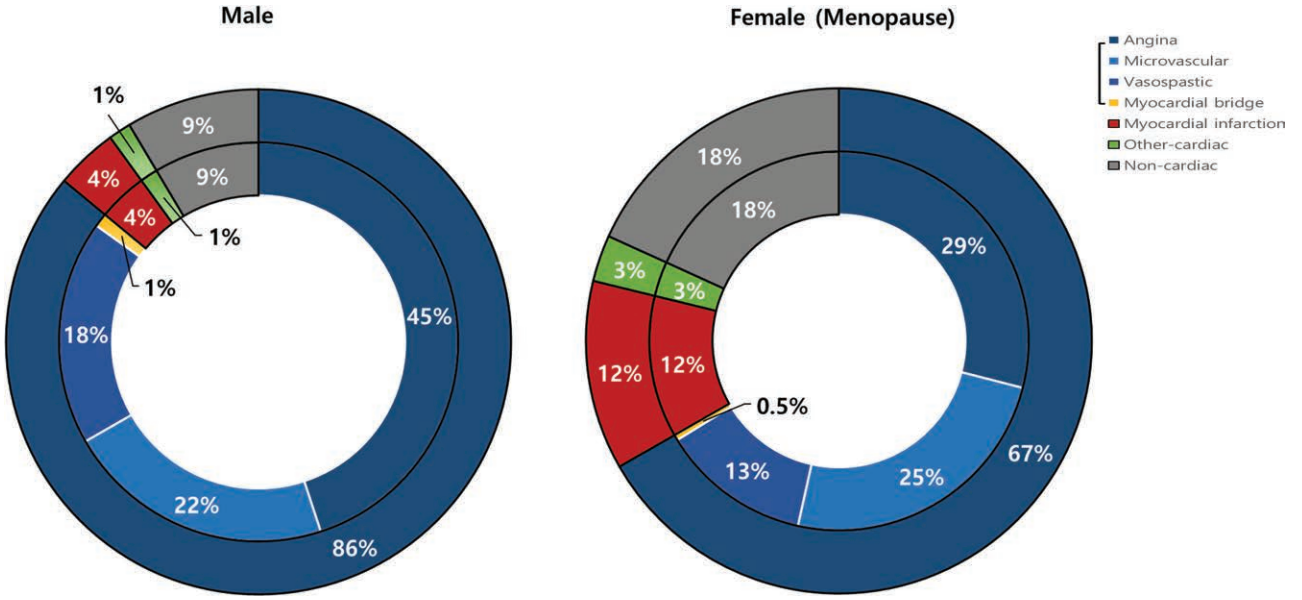
Multivariate analyses showed that b-CAD was related to age, DM, use of aspirin, current smoking and presence of RWMA (Table 3). HDL cholesterol level was related to a decreased odds ratio (OR) of 0.98 [95% confidence interval (CI): 0.97–0.99; $P < 0.001$]. Among these variables, age, DM and HDL cholesterol levels were associated with revascularization (Table 3). In men, b-CAD was associated with age, DM, HDL cholesterol, use of statins, use of aspirin, current smoking and presence of RWMA (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/MCA/A649*). Revascularization in men was associated with age, DM and HDL cholesterol levels. In menopausal women, b-CAD was associated with age, DM, HDL cholesterol level and use of aspirin (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/MCA/A649*). Revascularization in women was associated with hypertension. Early menopause was not related to b-CAD or revascularization ($P = 0.317$ and $P = 0.100$, respectively).

### Secondary composite cardiovascular outcomes

Secondary outcomes included admission for acute coronary syndrome, coronary revascularization, heart failure or stroke during follow-up. Death was defined as death due to any cause.

Univariate analyses (Supplementary Table 5, Supplemental digital content 1, *http://links.lww.com/MCA/A649*) showed that sex; systolic BP; hypertension; glycated hemoglobin; and use of hypoglycemic agents, statins and antiplatelet agents were associated with increased secondary outcomes. HDL cholesterol levels were not related to the secondary outcomes.

**Fig. 1**




Proportion of diseases according to sex. Angina pectoris, which is represented by the outer circle, was the most common symptom in both groups (men: $n = 775$, 86%; postmenopausal women: $n = 1008$, 67%). The angina pectoris was subclassified and represented in the inner circle in terms of frequency: (atherosclerotic, obstructive) angina, microvascular angina, vasospastic angina and myocardial bridge for both groups. Other cardiac diseases included arrhythmia, cardiomyopathy, heart failure, pericarditis and primary pulmonary hypertension. Noncardiac diseases include gastrointestinal, musculoskeletal and psychological problems.

**Table 3 Multivariate associations between basic characteristics and primary outcomes**

| | Binary CAD | | | Revascularization | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Sex (postmenopause female) | 0.76 | 0.56–1.04 | 0.088 | 0.72 | 0.49–1.08 | 0.113 |
| Age | 1.05 | 1.03–1.06 | <0.001 | 1.02 | 1.00–1.03 | 0.036 |
| Diabetes | 2.15 | 1.64–2.82 | <0.001 | 1.71 | 1.21–2.40 | 0.002 |
| Hypertension | 0.95 | 0.74–1.21 | 0.671 | 1.01 | 0.72–1.41 | 0.975 |
| HDL cholesterol | 0.98 | 0.97–0.99 | <0.001 | 0.98 | 0.97–1.00 | 0.008 |
| Statin | 1.16 | 0.89–1.50 | 0.270 | 1.17 | 0.83–1.66 | 0.379 |
| Aspirin | 1.95 | 1.51–2.53 | <0.001 | 1.19 | 0.84–1.68 | 0.333 |
| Smoking | | | | | | |
| Never | ref | | | ref | | |
| Current | 2.06 | 1.40–3.02 | <0.001 | 1.37 | 0.86–2.20 | 0.190 |
| Former | 1.12 | 0.73–1.74 | 0.603 | 0.69 | 0.38–1.26 | 0.222 |
| RWMA | 2.21 | 1.49–3.29 | <0.001 | 1.27 | 0.81–1.97 | 0.298 |

CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; RWMA, regional wall motion abnormality.

The multivariate analyses showed that secondary outcomes, including death, were only related to sex (OR: 0.55; 95% CI: 0.31–0.98; $P = 0.041$; Table 4). During the follow-up period, 16 patients underwent repeat PCI (6 men, 10 postmenopausal women) after the index PCI, and one man underwent PCI thrice (Supplementary Table 6, Supplemental digital content 1, *http://links.lww.com/MCA/A649*). During follow-up, men experienced 33 secondary outcomes and two deaths, whereas postmenopausal women experienced 33 secondary outcomes and one death. Supplementary Table 7, Supplemental digital content 1, *http://links.lww.com/MCA/A649* shows the detailed causes of the secondary outcomes.

### Propensity-matched primary and secondary outcomes

A total of 830 population, 415 both men and postmenopausal women were matched. The age of both groups was the same as 63.6 ± 8.9 years. Primary outcomes from the propensity-matched population (Table 5) were similar to Table 3. However, there were some differences. Male sex was appeared to be associated with b-CAG (OR: 0.61; 95% CI: 0.45–0.83; $P = 0.002$), which may be related to an increase in male age from 59.5 to 63.6 years after propensity matching. RWMA was found to be statistically significant in relation to revascularization (OR: 2.30; 95% CI: 1.34–3.97; $P = 0.002$).

Secondary outcomes, including death, were only related to sex (OR: 0.33; 95% CI: 0.13–0.85; $P = 0.022$; Table 6) which were the same as Table 4.

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**Table 4** **Multivariate associations between basic characteristics and secondary composite cardiovascular outcomes**

| | Secondary outcomes | | | Secondary outcomes + death | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Sex (Menopause women) | 0.55 | 0.31–0.98 | 0.041 | 0.52 | 0.30–0.92 | 0.024 |
| Age | 1.01 | 0.98–1.04 | 0.430 | 1.02 | 0.99–1.05 | 0.314 |
| Diabetes | 1.46 | 0.82–2.59 | 0.197 | 1.43 | 0.81–2.53 | 0.216 |
| Hypertension | 1.72 | 0.91–3.25 | 0.096 | 1.62 | 0.87–3.03 | 0.129 |
| Statin | 1.44 | 0.74–2.80 | 0.279 | 1.38 | 0.72–2.65 | 0.329 |
| Aspirin | 1.89 | 0.99–3.59 | 0.053 | 1.82 | 0.96–3.43 | 0.065 |

CI, confidence interval; OR, odds ratio.

**Table 5** **Multivariate associations between basic characteristics and primary outcomes using propensity-matched population**

| | Binary CAD | | | Revascularization | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Sex (postmenopause female) | 0.61 | 0.45–0.83 | 0.002 | 0.80 | 0.52–1.24 | 0.328 |
| Age | 1.05 | 1.03–1.06 | <0.001 | 1.02 | 1.00–1.04 | 0.152 |
| Diabetes | 2.60 | 1.80–3.75 | <0.001 | 1.98 | 1.22–3.21 | 0.006 |
| Hypertension | 0.83 | 0.59–1.18 | 0.303 | 0.62 | 0.38–1.01 | 0.054 |
| HDL cholesterol | 0.99 | 0.97–1.00 | 0.050 | 0.96 | 0.94–0.99 | 0.003 |
| Statin | 1.02 | 0.70–1.49 | 0.918 | 0.91 | 0.54–1.54 | 0.729 |
| Aspirin | 2.04 | 1.39–2.98 | <0.001 | 0.98 | 0.57–1.69 | 0.952 |
| Smoking | | | | | | |
| Never | ref | | | ref | | |
| Current | 1.68 | 0.95–2.96 | 0.073 | 1.08 | 0.51–2.28 | 0.841 |
| Former | 0.96 | 0.54–1.73 | 0.900 | 1.16 | 0.56–2.41 | 0.697 |
| RWMA | 2.61 | 1.62–4.21 | <0.001 | 2.30 | 1.34–3.97 | 0.003 |

CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; RWMA, regional wall motion abnormality.

**Table 6** **Multivariate associations between basic characteristics and secondary composite cardiovascular outcomes using propensity-matched population**

| | Secondary outcomes | | | Secondary outcomes + death | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Sex (Menopause women) | 0.35 | 0.13–0.92 | 0.033 | 0.33 | 0.13–0.85 | 0.022 |
| Age | 1.00 | 0.95–1.05 | 0.921 | 1.00 | 0.96–1.06 | 0.712 |
| Diabetes | 1.36 | 0.55–3.38 | 0.507 | 1.31 | 0.53–3.21 | 0.556 |
| Hypertension | 1.71 | 0.62–4.71 | 0.302 | 1.48 | 0.56–3.90 | 0.424 |
| Statin | 0.80 | 0.27–2.36 | 0.690 | 0.76 | 0.27–2.14 | 0.600 |
| Aspirin | 2.09 | 0.67–6.53 | 0.205 | 1.87 | 0.63–5.62 | 0.262 |

CI, confidence interval; OR, odds ratio.

## Discussion

On the basis of data from the KoROSE, this study showed the diagnosis, treatment and prognosis of both men and postmenopausal women who underwent invasive CAG for stable chest pain. The average age of postmenopausal women was approximately 7 years higher than that of men. On index CAG at study enrollment, men had a higher prevalence of b-CAD and number of revascularization procedures than that in postmenopausal women despite their younger age. Multivariate analysis showed that b-CAD and revascularization were related to age; comorbidities, such as diabetes; and HDL cholesterol levels but not to sex. Although age was adjusted in the multivariate analysis, there was a large age difference between men and women in baseline characteristics, so propensity matching was performed to exclude this, and the results showed that b-CAD was significantly increased in men. However, there was still no differences in revascularization between men and women. Interestingly, sex was associated with secondary composite cardiovascular outcomes during the follow-up period rather than primary outcomes (revascularization) at the time of patient enrollment. Sex was the only significant variable for secondary outcomes in this study.

Atherosclerosis is the main contributor to CVD. Endothelial dysfunction and the activation of inflammatory pathways play a role in the progression of atherosclerosis, which is characterized by lipid accumulation and fibrous plaque formation [30]. The atheroma plaque can cause plaque rupture and narrow the vessel lumen. Atherosclerotic CVD is common in both men and women, whereas nonatherosclerotic and nonobstructive ischemic heart disease are more common in women than in men [7]. Previous research results suggest that coronary microvascular dysfunction is one of the causes of nonobstructive myocardial ischemia [31]. An autopsy study showed

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that women had a greater frequency of plaque erosion and distal microvascular embolization, as well as a greater rate of embolization independent of thrombus type or presence of necrosis, than men [31,32]. A recent study showed that plaque rupture and vulnerability increased with age in women but not in men [33].

Some authors have reported that marital status; hormone replacement therapy; and reproductive history such as multigravida status, reproductive life span and time since menopause might have implications for CAD in postmenopausal women [21,34,35]. However, in the current study, these detailed histories were not investigated. Given that menopausal transition affects the increase in coronary heart disease and that many women develop CVD after menopause [36], the current study was conducted only in postmenopausal women. Approximately 10% of women are known to experience menopause before the age of 45 [36]. A total of 134 (8.87%) women experienced menopause at or before the age of 45 years, and this premature menopause did not reach statistical significance for either primary or secondary outcomes. This might be due to the small number of women who experienced early menopause.

Differences between men and women can also be found in the diagnoses of patients enrolled in this registry. The most common diagnosis was angina pectoris in both men and women. Interestingly, postmenopausal women have more serious diseases (e.g. myocardial infarction) and nonserious diseases (e.g. esophagitis) than men do. In other words, female patients have more noncardiac diseases that are less severe than those observed in male patients, and there is a chance that doctors who see such patients will not make active efforts toward diagnosis and treatment. However, postmenopausal women have a higher rate of myocardial infarction and noncardiac diseases than those observed in men. Therefore, it is important to understand the disease characteristics in postmenopausal women who are visiting outpatient clinics for chest pain.

Women with CVD have a similar or worse prognosis than those of men because they are older and have more risk factors than men do [37,38]. This finding can be attributed to several factors: women visit the hospital later than men do (patient delay) [39], women are less likely to undergo revascularization than men are (system delay) [40] and women are less likely to be treated with optimal medical therapy for secondary prevention [39,41].

Contrary to the results from previous studies, this study showed that women (particularly postmenopausal women) had an OR of 0.55 (95% CI: 0.31–0.98; $P = 0.041$) for the secondary outcomes when compared with men. This result consistent after age-matched analysis (OR: 0.35; 95% CI: 0.13–0.92; $P = 0.033$). Therefore, these results are clinically significant. This study was performed using data from the KoROSE, which was constructed to investigate Korean women who underwent CAG with suspected CAD in a stable condition. Therefore, this study has a different starting point from previous studies in that women are less likely to undergo invasive procedures than men are. All female patients enrolled in this study had the same starting point as the male patients without gender bias, which is sometimes observed in real-world practice. Furthermore, multivariate analyses from this study found no difference in primary outcomes, namely, revascularization, between postmenopausal women and men. Postmenopausal women had a lower rate of secondary composite outcomes than that in men during the follow-up period. Hence, postmenopausal women have the same risk of b-CAD and revascularization as men but will have better clinical outcomes than those of men if they receive optimal treatment.

Active medical intervention by improving the awareness of women's heart disease can improve prognoses. The Federal government and American Heart Association reduced CVD mortality by nearly half from 1997 to 2007 via an active campaign for women heart [1].

Despite its clinical significance, this study has several limitations. This was a multicenter registry study in which the patient population and procedures may not be uniform, and there is potential for selection bias. The term 'stable chest pain' is heterogeneous and implies stable coronary artery disease or chronic coronary syndrome (CCS). CCS is also a heterogeneous disease entity, and the European Society of Cardiology guidelines describe CCS by using the most frequently encountered clinical scenarios rather than a single definition [17]. This study involved only postmenopausal women; therefore, it will be difficult to generalize our results to all women.

## Conclusions

Postmenopausal women who visited an outpatient clinic with stable chest pain and underwent invasive CAG were comparable to men in terms of the prevalence of b-CAD and number of revascularization procedures even though such women were 7 years older than the men. However, secondary composite cardiovascular events are less common in postmenopausal women than in men. Hence, it is important to accurately diagnose and treat chest pain in postmenopausal women, which is expected to improve their prognosis.

## Acknowledgements

None.

S.K.: conceptualization, data curation, writing, original draft and editing. M.-S.S.: investigation, methodology, project administration, supervision, writing, review and editing. H.A.L.: formal analysis, data curation, writing, review and editing. M.-N.K.: investigation and methodology. H.-L.K.: investigation and supervision. H.-J.Y.: project administration and investigation. S.-M.P.: investigation, methodology and conceptualization.

K.-S.H.: investigation and methodology. M.-A.L.: supervision and investigation.

### Conflicts of interest

There are no conflicts of interest.

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