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Sex differences in coronary angiographic findings in patients with stable chest pain: analysis of data from the KoRean wOmen'S chest pain rEgistry (KoROSE)

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Abstract

Background: Focused evaluations on potential sex differences in the angiographic findings of the coronary arteries are scarce. This study was performed to compare the angiographic extent and localization of coronary stenosis between men and women.

Methods: A total of 2348 patients (mean age 62.5 years and 60% women) with stable chest pain undergoing invasive coronary angiography (CAG) were recruited from the database of the nation-wide chest pain registry. Obstructive coronary artery disease (CAD) was defined as $\geq 50\%$ stenosis of the left main coronary artery and/or $\geq 70\%$ stenosis of any other epicardial coronary arteries.

Results: Although women were older than men (64.4 ± 10.3 vs. 59.5 ± 11.4 years, $P < 0.001$), men had worse risk profiles including high blood pressure, more frequent smoking and elevated triglyceride and C-reactive protein. The prevalence of obstructive CAD was significantly higher in men than in women (37.0% vs. 28.4%, $P < 0.001$). Men had a higher prevalence of LM disease (10.3% vs. 3.5%, $P < 0.001$) and three-vessel disease (16.1% vs. 9.5%, $P = 0.007$) compared to women. In multiple binary logistic regression analysis, the risk of men having LM disease or three-vessel disease was 7.4 (95% confidence interval 3.48–15.97; $P < 0.001$) and 2.7 (95% confidence interval 1.57–4.64; $P < 0.001$) times that of women, respectively, even after controlling for potential confounders.

Conclusions: In patients with chest pain undergoing invasive CAG, men had higher obstructive CAD prevalence and more high-risk angiographic findings such as LM disease or three-vessel disease.

Highlights

- Focused evaluation on sex differences in the angiographic findings of the coronary arteries is limited.
- We evaluated sex differences in the angiographic extent and localization of coronary stenosis in 2348 patients.

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- Men had higher prevalence of obstructive coronary artery disease and more high-risk angiographic findings such as left main disease or three-vessel disease.
- This sex difference could be applied in the clinical evaluation and management of patients with suspected coronary artery disease.

Keywords: Coronary angiography, Coronary artery disease, Left main disease, Sex differences, Three-vessel disease

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. With improvement in diagnostic and therapeutic tools, the prognosis of patients with CAD has been much improved. However, the prevalence of CAD is still high, and the complications associated with CAD are the number one cause of human death [1–3]. Therefore, in order to improve patients' prognosis and reduce the enormous medical cost, it is important to find CAD patients earlier and perform customized treatment. For rapid CAD diagnosis and effective treatment, understanding pathophysiology underlying in CAD development should be the basis. Human efforts to understand sex differences in the cardiovascular field, and to apply them in clinical practice have continued [4–6]. In CAD, sex differences in several points such as clinical presentation and prognosis are relatively well evaluated. However, little is known regarding potential sex differences in the angiographic findings of coronary arteries. Since invasive coronary angiography (CAG) is the reference standard for CAD diagnosis, understanding sex difference in invasive CAG findings is valuable for the management of patients with CAD. Therefore, this study was performed to compare the extent and localization of coronary stenosis on invasive CAG between men and women.

Materials and methods

Study patients

We analyzed data from the nation-wide prospective registry database, the KoRean wOmen'S chest pain rEgistry (KoROSE), which was constructed to investigate clinical characteristics and outcomes of Korean women with suspected CAD in a stable state. For comparison, men were also registered in the registry. Many research articles using this registry data have already been published [7–9]. Collection of this registry data began in February 2011, and patient registration is still ongoing. Currently, 22 cardiovascular centers in Korea are participating in this registry. The patients enrolled were Korean adult men and women over the age of 20 years who complained of chest pain and underwent invasive CAG because of suspected CAD. Because study enrollment was based on

relatively stable patients who visited the outpatient clinic, patients with acute coronary syndrome were excluded. In most cases, tests such as treadmill exercise test, coronary computed tomography angiography, single-photon emission computed tomography, and dobutamine stress echocardiography were performed according to the patient's renal function and functional capacity. Invasive CAG was performed according to these results of non-invasive tests. After invasive CAG, attending physician explained the study protocol and enrolled patients who agreed to participate in the registry. The Institutional Review Board of Boramae Medical Center (Seoul, South Korea) approved registry registration, and the use of the registered data for research purposes. All patients were given written consent for registry registration.

Data collection

Clinical data were obtained at the time of admission for invasive CAG. Body mass index was the body weight (kg) divided by the height squared (m^2). Body mass index ≥ 25 kg/m^2 was considered obese [10]. Waist circumference was measured with a tape measure. A tape measure was placed in the middle of the lowest position of the ribs and the highest position of the pelvis during expiration. Systolic/diastolic blood pressure and heart rate were measured by a trained nurse using an automatic oscillometric device. Hypertension was defined on the basis of (1) previous diagnosis of hypertension by a physician; (2) current anti-hypertensive medications, or (3) systolic/diastolic blood pressure $\geq 140/90$ mmHg in repeated measurements. Diabetes mellitus was defined on the basis of (1) previous diagnosis of diabetes mellitus by a physician; (2) current anti-diabetic medications, or (3) fasting blood glucose level ≥ 126 mg/dL in repeated tests. Dyslipidemia was defined on the basis of (1) previous diagnosis of dyslipidemia by a physician; (2) current anti-dyslipidemic medications, or (3) low-density lipoprotein cholesterol ≥ 160 mg/dL. A person who smoked regularly within the last 12 months was defined as a smoker. After overnight fasting, blood levels of the following laboratory parameters were obtained: white blood cell count, hemoglobin, creatinine, glucose, glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride,

and C-reactive protein. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation. Information on concomitant cardiovascular medications including antiplatelets, calcium channel blocker, beta-blocker, renin-angiotensin system blocker, and statin was also obtained.

Invasive CAG

Invasive CAG was performed using a radial or femoral artery in accordance with current guidelines [11, 12]. All management strategies for CAD, including coronary revascularization, were chosen at the discretion of the attending physician. An obstructive CAD was defined as any $\geq 50\%$ stenosis of the left main coronary artery, $\geq 70\%$ stenosis of any other epicardial coronary arteries, or both. The extent of CAD was classified as one-, two-, or three-vessel disease. Significant left main stenosis ($\geq 50\%$) was considered as two-vessel diseases. The coronary artery was divided into 17 segments, and we obtained information on the maximum stenosis of each segment [13, 14]. Left main disease or three-vessel disease were considered as a high-risk finding.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation, and categorical variables are expressed as n (%). Student's t test was used to compare continuous variables and the Chi-square test was used to compare categorical variables between two groups. Binary logistic regression analyses were performed to investigate independent associations between sex and angiographic findings. During multivariable analyses the following potential confounders were controlled: age, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking and renal function. A P value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics of the study patients

Nine hundred and forty-one men and 1407 women (59.9%) were analyzed in this study. Comparisons of clinical characteristics between men and women are demonstrated in Table 1. Women were older than men (64.4 ± 10.3 vs. 59.5 ± 11.4 years, $P < 0.001$). Mean body mass index was similar between men and women, but waist circumference was greater in men than in women. Both systolic and diastolic blood pressures were higher in men than in women. Among traditional cardiovascular risk factors, the proportions of smokers and obesity were higher in men than in women. In laboratory findings, women had lower blood hemoglobin, triglycerides and

C-reactive protein levels as well as higher total cholesterol and high-density lipoprotein cholesterol levels than men. Among cardiovascular medications, beta-blockers and statin were more frequently prescribed in women than in men.

About one-third of patients (31.8%) had obstructive CAD. Comparisons of clinical characteristics between patients with and without obstructive CAD in men and women are shown in Table 2. Patients with obstructive CAD were older in both men (62.6 ± 10.2 vs. 57.0 ± 11.6 years, $P < 0.001$) and women (68.1 ± 9.1 vs. 62.4 ± 10.3 years, $P < 0.001$). Patients with obstructive CAD had more cardiovascular risk factors such as hypertension, diabetes and smoking than those without in both sexes. Laboratory findings also showed worse profiles including higher levels of white blood cell count, fasting glucose and low-density lipoprotein cholesterol as well as lower levels of hemoglobin, glomerular filtration rate, and high-density lipoprotein cholesterol in patients with obstructive CAD than in those without in both men and women. Antiplatelets, beta-blocker, renin-angiotensin system blocker and statin were more frequently prescribed to patients with obstructive CAD than those without in both sexes.

Sex differences in angiographic findings

Angiographic findings of men and women in the total study population are demonstrated in Table 3. The prevalence of obstructive CAD was significantly higher in men than in women (37.0% vs. 28.4%, $P < 0.001$) (Fig. 1). Two- or three-vessel disease or LM disease was more prevalent in men than in women (16.0% vs. 11.2%, $P \leq 0.001$). In addition to the three major epicardial coronary arteries, significant stenosis of the branch arteries was also prevalent in men, compared to women. LM disease with proximal LAD significant stenosis or LM with proximal significant stenosis of at least one of three major epicardial coronary arteries were more frequently observed in men than in women. Even when we considered only patients with obstructive CAD, men had more three-vessel disease or LM disease than in women ($P < 0.05$ for each) (Fig. 2). Significant stenosis of the RCA and branched coronary arteries were more prevalent in men than in women (Table 4). Being a man itself was an independent factor predicting obstructive CAD (OR [odds ratio] 1.48; 95% CI [confidence interval] 1.17–1.86; $P = 0.001$), LM disease (OR 7.46; 95% CI 3.48–15.98; $P < 0.001$), LM disease with proximal LAD significant stenosis (OR 1.51; 95% CI 1.16–1.98; $P = 0.002$), and three-vessel disease (OR 2.70; 95% CI 1.57–4.64; $P < 0.001$), even though various clinically important covariates were corrected (Table 5). Besides male sex, old age was associated with LM disease, and old age, hypertension and diabetes mellitus were associated with three-vessel disease

Table 1 Clinical characteristics of study patients according to sex

| Characteristic | Men (n = 941) | Women (n = 1407) | P value |
|--|------------------|---------------------|---------|
| Age, years | 59.5 ± 11.4 | 64.4 ± 10.3 | < 0.001 |
| Body mass index, kg/m ² | 25.1 ± 3.1 | 25.1 ± 3.7 | 0.905 |
| Body mass index ≥ 25 kg/m ² , % | 51.5 | 46.2 | 0.014 |
| Waist circumference (WC), cm | 86.7 ± 9.5 | 82.7 ± 10.0 | < 0.001 |
| WC ≥ 90 cm for men and ≥ 85 cm for women, % | 35.9 | 38.6 | 0.348 |
| Systolic blood pressure, mmHg | 128 ± 17 | 126 ± 18 | 0.025 |
| Diastolic blood pressure, mmHg | 79.0 ± 11.6 | 75.4 ± 11.6 | < 0.001 |
| Heart rate, per minute | 74.7 ± 13.6 | 74.5 ± 12.7 | 0.782 |
| Cardiovascular risk factors, % | | | |
| Hypertension | 53.6 | 56.0 | 0.255 |
| Diabetes mellitus | 27.0 | 23.9 | 0.110 |
| Dyslipidemia | 25.2 | 26.7 | 0.491 |
| Current smoking | 35.0 | 4.9 | < 0.001 |
| Obesity (body mass index ≥ 25 kg/m ²) | 51.5 | 46.2 | 0.014 |
| Laboratory findings | | | |
| White blood cell count, per microliter | 6951 ± 2118 | 6811 ± 2647 | 0.197 |
| Hemoglobin, g/dL | 14.3 ± 1.6 | 12.8 ± 1.4 | < 0.001 |
| Glomerular filtration rate, mL/min/1.73 m ² | 81.5 ± 21.3 | 83.3 ± 29.1 | 0.102 |
| Fasting glucose, mg/dL | 119 ± 44 | 118 ± 46 | 0.755 |
| Glycated hemoglobin, % | 6.25 ± 1.25 | 6.17 ± 1.12 | 0.356 |
| Total cholesterol, mg/dL | 164 ± 41 | 172 ± 44 | < 0.001 |
| Low-density lipoprotein cholesterol, mg/dL | 101 ± 36 | 103 ± 36 | 0.156 |
| High-density lipoprotein cholesterol, mg/dL | 43.6 ± 11.6 | 49.3 ± 13.2 | < 0.001 |
| Triglycerides, mg/dL | 154 ± 111 | 127 ± 87 | < 0.001 |
| C-reactive protein, mg/dL | 2.12 ± 8.83 | 0.97 ± 3.24 | 0.007 |
| Concomitant medications, % | | | |
| Antiplatelets | 48.8 | 51.2 | 0.287 |
| Calcium channel blocker | 33.7 | 34.0 | 0.896 |
| Beta-blocker | 23.1 | 29.2 | 0.003 |
| Renin-angiotensin system blocker | 39.3 | 39.6 | 0.874 |
| Statin | 51.4 | 56.6 | 0.022 |

even after controlling for potential confounders (Additional file 1: Table S1).

Discussion

Using a nation-wide registry database, we attempted to find out the sex differences of invasive CAG findings in patients who had chest pain in a stable state. Our results showed several important findings: (1) despite younger age, men more frequently had risk factors for cardiovascular disease than women, which resulted in a higher obstructive CAD prevalence in men; (2) men more frequently had LM disease or three-vessel disease than women, and (3) these sex differences persisted even after controlling for important clinical covariates.

Previous similar studies

The summary of previous studies investigating sex differences in CAG findings is demonstrated in Table 6. Numerous studies have reported that angiographically documented CAD is more severe in men than in women [15–22]. These findings are concordant with ours showing that compared to women, men had more burden of obstructive CAD. However, our study has several differences and strengths compared to the previous studies. Most of the existing studies were conducted in the Western countries. If we consider ethnic differences in cardiovascular disease [23], our study of Koreans is valuable. Our study provides an additional result that in Asians like Westerners, men more frequently have CAD than women. Considering very low proportion of women in previous studies, higher proportion of women was

Table 2 Clinical characteristics of study patients according to the presence of obstructive CAD and sex

| Characteristic | Men (n = 941) | | | Women (n = 1407) | | |
|---------------------------------------|-------------------------------|-------------------------------|---------|-------------------------------|-------------------------------|---------|
| | Obstructive CAD (–) (n = 517) | Obstructive CAD (+) (n = 424) | P value | Obstructive CAD (–) (n = 907) | Obstructive CAD (+) (n = 500) | P value |
| Age, years | 57.0 ± 11.6 | 62.6 ± 10.2 | < 0.001 | 62.4 ± 10.3 | 68.1 ± 9.1 | < 0.001 |
| BMI, kg/m ² | 25.0 ± 3.1 | 25.2 ± 3.1 | 0.536 | 25.1 ± 3.7 | 25.0 ± 3.7 | 0.389 |
| Waist circumference, cm | 86.0 ± 9.0 | 87.6 ± 10.1 | 0.082 | 82.0 ± 10.1 | 83.9 ± 9.6 | 0.016 |
| Systolic blood pressure, mmHg | 126 ± 16 | 130 ± 18 | 0.005 | 124 ± 17 | 130 ± 20 | < 0.001 |
| Diastolic blood pressure, mmHg | 79.7 ± 11.5 | 78.2 ± 11.7 | 0.088 | 75.1 ± 11.3 | 76.1 ± 12.2 | 0.188 |
| Heart rate, per minute | 75.1 ± 13.9 | 74.3 ± 13.2 | 0.426 | 74.2 ± 12.2 | 74.9 ± 13.5 | 0.418 |
| Cardiovascular risk factors, % | | | | | | |
| Hypertension | 47.4 | 61.1 | < 0.001 | 49.3 | 67.7 | < 0.001 |
| Diabetes mellitus | 19.6 | 36.2 | < 0.001 | 17.8 | 34.6 | < 0.001 |
| Dyslipidemia | 26.0 | 24.5 | 0.653 | 27.3 | 25.6 | 0.526 |
| Current smoking | 31.5 | 39.1 | 0.021 | 4.9 | 4.8 | 0.972 |
| Obesity (BMI ≥ 25 kg/m ²) | 51.1 | 52.0 | 0.807 | 46.0 | 46.4 | 0.889 |
| Laboratory findings | | | | | | |
| WBC, per microliter | 6764 ± 2118 | 7175 ± 2098 | 0.005 | 6471 ± 2237 | 7405 ± 3156 | < 0.001 |
| Hemoglobin, g/dL | 14.5 ± 1.5 | 14.0 ± 1.6 | < 0.001 | 12.9 ± 1.3 | 12.5 ± 1.6 | < 0.001 |
| GFR, mL/min/1.73 m ² | 82.1 ± 19.4 | 80.8 ± 23.4 | 0.356 | 84.1 ± 27.5 | 81.9 ± 31.6 | 0.204 |
| Fasting glucose, mg/dL | 113 ± 36 | 127 ± 52 | < 0.001 | 112 ± 40 | 129 ± 53 | < 0.001 |
| Glycated hemoglobin, % | 5.97 ± 1.05 | 6.58 ± 1.38 | < 0.001 | 6.04 ± 0.99 | 6.39 ± 1.26 | < 0.001 |
| Total cholesterol, mg/dL | 165 ± 40 | 162 ± 43 | 0.218 | 171 ± 43 | 173 ± 46 | 0.491 |
| LDL cholesterol, mg/dL | 102 ± 34 | 100 ± 38 | 0.435 | 101 ± 35 | 107 ± 37 | 0.018 |
| HDL cholesterol, mg/dL | 45.2 ± 12.2 | 41.6 ± 10.6 | < 0.001 | 51.1 ± 13.9 | 45.8 ± 11.1 | < 0.001 |
| Triglyceride, mg/dL | 155 ± 108 | 152 ± 116 | 0.776 | 123 ± 75 | 133 ± 105 | 0.079 |
| C-reactive protein, mg/dL | 2.74 ± 11.5 | 1.39 ± 3.56 | 0.101 | 0.79 ± 2.47 | 1.28 ± 4.22 | 0.081 |
| Concomitant medications, % | | | | | | |
| Antiplatelet | 36.9 | 63.8 | < 0.001 | 43.1 | 65.9 | < 0.001 |
| Calcium channel blocker | 29.1 | 39.6 | 0.002 | 33.5 | 34.9 | 0.632 |
| Beta-blocker | 15.9 | 32.3 | < 0.001 | 23.5 | 39.8 | < 0.001 |
| RAS blocker | 33.0 | 47.3 | < 0.001 | 34.5 | 49.0 | < 0.001 |
| Statin | 42.6 | 62.7 | < 0.001 | 52.4 | 64.3 | < 0.001 |

CAD coronary artery disease; BMI body mass index; WBC white blood cell; GFR glomerular filtration rate; LDL low-density lipoprotein; HDL high-density lipoprotein; RAS renin-angiotensin system

another strength of this study. In addition, the primary research goal in most studies was to determine if there were sex differences in subsequent management and clinical outcomes following CAG. Therefore, only sex differences in CAG findings were demonstrated briefly, and more specific analysis on lesion location were not shown in most studies. Only one study focused primarily on sex differences in angiographic findings, and showed specific CAD locations [15]. Moreover, only a few studies have performed multivariable analysis to demonstrate whether sex is an independent factor associated with CAD severity [18, 22]. In our study, the primary aim was to determine the differences in CAG findings between men and women. In addition, we analyzed the detailed lesion location of CAD, and also performed multivariable analysis

to evaluate the effect of sex on CAD severity after adjustment for confounding factors. Although not the majority opinion, some other studies have shown that there is no sex difference in the extent and localization of coronary angiographic lesions [24–27]. Further studies are needed to reach a firmer conclusion on sex difference in the severity and extent of angiographic CAD.

Underlying mechanisms

In our study, higher blood pressure, greater proportions of smokers and obese patients, and worse lipid profiles could explain more significant and extensive CAD in men than in women. Although women were older than men, they less frequently had cardiovascular risk factors than men. Indeed, in addition to old age and male

Table 3 Angiographic findings according to sex in total population

| Characteristic | Men (n = 941) | Women (n = 1407) | P value |
|--|---------------|------------------|---------|
| Obstructive CAD (LM ≥ 50%, other ≥ 70%) | 348 (37.0) | 400 (28.4) | < 0.001 |
| Insignificant | 593 (63.0) | 1007 (71.6) | < 0.001 |
| One-vessel disease | 197 (20.9) | 242 (17.2) | |
| Two-vessel disease | 95 (10.1) | 120 (8.5) | |
| Three-vessel disease | 56 (6.0) | 38 (2.7) | |
| Two- or three-vessel disease | 151 (16.0) | 158 (11.2) | 0.001 |
| LM disease (≥ 50%) | 36 (3.8) | 14 (1.0) | < 0.001 |
| LAD stenosis | | | |
| Total LAD ≥ 70% | 233 (24.8) | 277 (19.7) | 0.003 |
| Proximal LAD ≥ 70% | 116 (12.3) | 140 (10.0) | 0.070 |
| Mid-LAD ≥ 70% | 101 (10.7) | 132 (9.4) | 0.283 |
| Distal LAD ≥ 70% | 19 (2.0) | 21 (1.5) | 0.334 |
| LCX stenosis | | | |
| Total LCX ≥ 70% | 140 (14.9) | 161 (11.4) | 0.015 |
| Proximal LCX ≥ 70% | 55 (5.8) | 59 (4.2) | 0.068 |
| Distal LCX ≥ 70% | 69 (7.3) | 94 (6.7) | 0.543 |
| RCA stenosis | | | |
| Total RCA ≥ 70% | 153 (16.3) | 147 (10.4) | < 0.001 |
| Proximal RCA ≥ 70% | 51 (5.4) | 52 (3.7) | 0.046 |
| Mid-RCA ≥ 70% | 51 (5.4) | 64 (4.5) | 0.338 |
| Distal RCA ≥ 70% | 50 (5.3) | 43 (3.1) | 0.006 |
| Branched artery stenosis | | | |
| Diagonal ≥ 70% | 45 (4.8) | 25 (1.8) | < 0.001 |
| OM ≥ 70% | 25 (2.7) | 12 (0.9) | 0.001 |
| PDA or PL ≥ 70% | 28 (3.0) | 13 (0.9) | < 0.001 |
| LM disease (≥ 50%) and pLAD stenosis (≥ 70%) | 244 (25.9) | 283 (20.1) | 0.001 |
| LM disease (≥ 50%) and proximal stenosis (≥ 70%) | 348 (37.0) | 400 (28.4) | < 0.001 |

Numbers are expressed as n (%)

CAD coronary artery disease; LM left main; LAD left anterior descending artery; LCX left circumflex artery; RCA right coronary artery; OM obtuse marginal artery; PDA posterior descending artery; PL posterior longitudinal artery

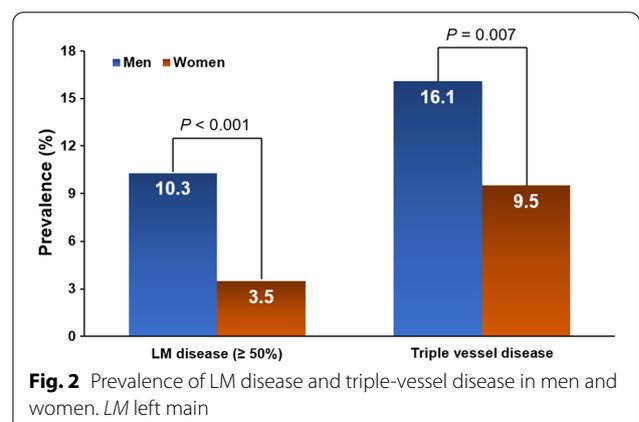
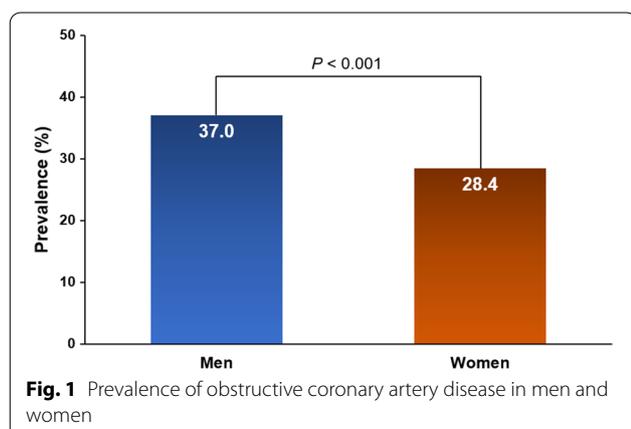


Table 4 Angiographic findings according to sex in patients with obstructive CAD

| Characteristic | Men (n = 348) | Women (n = 400) | P value |
|--|------------------|--------------------|---------|
| One-vessel disease | 197 (56.6) | 242 (60.5) | 0.025 |
| Two-vessel disease | 95 (27.3) | 120 (30.3) | |
| Three-vessel disease | 56 (16.1) | 38 (9.5) | |
| Two- or three-vessel disease | 151 (43.4) | 309 (41.3) | 0.281 |
| Three-vessel disease | 56 (16.1) | 38 (9.5) | 0.007 |
| LM disease (≥ 50%) | 36 (10.3) | 14 (3.5) | < 0.001 |
| LAD stenosis | | | |
| Total LAD ≥ 70% | 233 (67.0) | 277 (69.2) | 0.501 |
| Proximal LAD ≥ 70% | 116 (33.3) | 140 (35.0) | 0.632 |
| Mid-LAD ≥ 70% | 101 (29.0) | 132 (33.0) | 0.241 |
| Distal LAD ≥ 70% | 19 (5.5) | 21 (5.2) | 0.899 |
| LCX stenosis | | | |
| Total LCX ≥ 70% | 140 (40.2) | 161 (40.2) | 0.996 |
| Proximal LCX ≥ 70% | 55 (15.8) | 59 (14.8) | 0.689 |
| Distal LCX ≥ 70% | 69 (19.8) | 94 (23.5) | 0.225 |
| RCA stenosis | | | |
| Total RCA ≥ 70% | 153 (44.0) | 147 (36.8) | 0.045 |
| Proximal RCA ≥ 70% | 51 (14.7) | 52 (13.0) | 0.512 |
| Mid-RCA ≥ 70% | 51 (14.7) | 64 (16.0) | 0.611 |
| Distal RCA ≥ 70% | 50 (14.4) | 43 (10.8) | 0.135 |
| Branched artery stenosis | | | |
| Diagonal ≥ 70% | 45 (12.9) | 25 (6.2) | 0.002 |
| OM ≥ 70% | 25 (7.2) | 13 (3.0) | 0.008 |
| PDA or PL ≥ 70% | 28 (8.0) | 13 (3.2) | 0.004 |
| LM disease (≥ 50%) and pLAD stenosis (≥ 70%) | 244 (70.1) | 283 (70.8) | 0.849 |
| LM disease (≥ 50%) and proximal stenosis (≥ 70%) | 348 (100) | 400 (100) | 1.000 |

Numbers are expressed as n (%)

CAD coronary artery disease; LM left main; LAD left anterior descending artery; LCX left circumflex artery; RCA right coronary artery; OM obtuse marginal artery; PDA posterior descending artery; PL posterior longitudinal artery

Table 5 Association between sex and CAD

| Variable | OR (95% CI) | P value |
|--|------------------|---------|
| Obstructive CAD | | |
| Men (vs. women) | 1.50 (1.14–1.96) | 0.003 |
| LM disease (≥ 50%) | | |
| Men (vs. women) | 5.84 (2.55–13.3) | < 0.001 |
| LM disease (≥ 50%) and pLAD stenosis (≥ 70%) | | |
| Men (vs. women) | 1.56 (1.18–2.05) | 0.001 |
| Three-vessel disease | | |
| Men (vs. women) | 2.51 (1.37–4.60) | 0.003 |

Age, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, renal function, and the use of antiplatelet, beta-blocker, renin-angiotensin system blocker and statin were adjusted

CAD coronary artery disease; OR odds ratio; CI confidence interval; LM left main; LAD left anterior descending artery

sex, traditional cardiovascular risk factors including hypertension and diabetes mellitus were significantly associated with the presence of three-vessel disease in our multivariable analysis. However, old age and male sex were only factors associated with LM disease, and the risk of male sex itself was higher than age. It can be assumed that male sex itself had a great influence on LM disease, and cardiovascular risk factors, which have a high prevalence in men, contributed to the development of three-vessel disease. Cardiovascular system protection by female sex hormone may be a commonly proposed reason for lower risk profiles in women [28]. In our study, women had higher HDL-C than men, and those with CAD had significantly lower HDL-C than those without CAD. This result suggests that HDL-C probably played an important role in CAD development and progression [29], and induced sex differences.

Table 6 Summary of previous studies on sex differences in CAG findings

| Source | Area or country | Number of study subjects | Population | Female (%) | Primary research goal | Findings on sex difference of CAG findings |
|--------------------------------|-----------------|--------------------------|--------------------------------|------------|---|---|
| Giannoglou et al. [15] | Greece | 14,090 | Suspected CAD | 12.9 | To investigate sex differences of angiographic findings | Significant stenosis ($\geq 50\%$) were more common in men (86% vs. 64%; $P < 0.001$) than in women |
| Gudnadottir et al. [16] | Sweden | 106,881 | Acute coronary syndrome | 31.9 | To investigate gender disparities in revascularization and clinical outcomes | Both left main stem stenosis and three-vessel disease were more common in men than in women (30.4% vs. 20.9%; $P < 0.001$) |
| Ouellette et al. [17] | USA | 925 | Suspected CAD | 44.4 | To investigate clinical characteristics and outcome of normal or near-normal coronary artery stenosis | More women than men (53.5% vs. 37.2%; $P < 0.001$) had normal or near-normal coronary arteries or non-obstructive CAD |
| Patel et al. [18] | USA | 397,954 | Suspected CAD | 47.3 | To investigate the diagnostic yield of invasive CAG | Male sex was an independent predictor for obstructive CAD (adjust OR 2.70; 95% CI 2.64–2.76) |
| Ritsinger et al. [19] | Sweden | 2776 | Type 1 diabetes undergoing CAG | 42.0 | To investigate sex aspects on CAD extent and prognosis in patients with type 1 diabetes | Three-vessel disease or left main disease were more common in men than in women (40.4% vs. 34.5%; $P = 0.002$) |
| Chiha et al. [20] | Australia | 994 | Suspected CAD | 28.0 | To investigate sex difference in CAG findings | Compared to men, women had lower mean extent scores (19.6 vs. 36.8; $P < 0.0001$) and lower vessel scores (0.7 vs. 1.3; $P < 0.0001$) |
| Bell et al. [21] | USA | 22,795 | Suspected CAD | 17.3 | To investigate gender bias in the selection for revascularization | Three-vessel disease was more frequently observed in men compared to women (41% vs. 26%, $P < 0.0001$) |
| Tamis-Holland et al. [22] | USA | 1775 | Type 2 diabetes with CAD | 30.0 | To investigate gender differences in symptoms and extent of CAD | Number of significant lesions was higher (2.7 ± 1.8 vs. 2.3 ± 1.7 ; $P < 0.001$) and total occlusion were more common (42% vs. 29%; $P < 0.001$) in men than in women |
| Roeters van Lennep et al. [24] | Netherlands | 1894 | With documented CAD | 19.4 | To investigate gender-related differences in CAD extent and localization | There were no significant differences in the prevalence of three-vessel disease (31.8% vs. 29.4%) and left main disease (6.4% vs. 8.1%) between men and women ($P = 0.839$) |
| Leaf et al. [25] | USA | 1187 | Suspected CAD | 21.6 | To investigate sex difference in CAG findings | There were no significant differences in the prevalence of three-vessel disease (47.5% vs. 42.9%) and left main disease (8.6% vs. 8.6%) between men and women in patients with CAD ($P > 0.05$) |

Table 6 (continued)

| Source | Area or country | Number of study subjects | Population | Female (%) | Primary research goal | Findings on sex difference of CAG findings |
|-------------------------|-----------------|--------------------------|--|------------|--|---|
| Kyridakidis et al. [26] | Greece | 735 | With documented CAD | 26.1 | To investigate sex difference in CAG findings | Three-vessel CAD less common in women than in men (16% vs. 35%; $P < 0.001$). Gensini index was significantly higher in men (59 vs. 52; $P = 0.03$). The location of coronary stenoses did not show differences between men and women |
| Kim et al. [27] | South Korea | 1136 | Patients who underwent fractional flow reserve measurement | 26.4 | To investigate the influence of sex on the relationship between total anatomical and physiologic disease burdens | There were no differences in angiographic diameter stenosis, SYNTAX score, or residual SYNTAX score between women and men |

CAG coronary angiography; CAD coronary artery disease; OR odds ratio; CI confidence interval; SYNTAX synergy between percutaneous coronary intervention with Taxus and cardiac surgery

Clinical implications

Our results of Asian patients did not differ significantly from the main finding of the existing Western studies indicating that men had a more severe angiographically documented CAD than women. We should always be aware of the high risk of male sex itself when treating patients. In other words, since women generally develop less coronary artery pathology compared to men at the same age, women with CAD represent a vulnerable subgroup and need special attention. In addition, given that men have more severe and extensive CAD, one can expect that women have less symptoms and better prognosis; however, previous studies have shown opposite findings [30]. As ischemia and ischemia-like symptoms are not solely related to the severity of atherosclerosis, we should not overlook the fact that coronary microvascular dysfunction or coronary spasm are a more common cause of stable ischemic heart disease in women [5, 6, 26].

Study limitations

We acknowledge several limitations of the present study. First, coronary stenosis was visually evaluated in our study. If we had performed quantitative coronary analysis, more accurate data could have been obtained. Second, in our study, no intravascular evaluation or computed tomographic examination was performed, so we could not analyze differences between men and women in coronary plaque properties [4, 5, 31]. Third, the hemodynamical significance of CAD was not evaluated in our study. Lastly, since all subjects of our study were Koreans and patients with stable chest pain, it would be difficult to apply our results directly to other ethnic groups or patients with acute coronary syndrome.

Perspectives and significance

Among Korean patients with chest pain in a stable state, men had more extensive and severe angiographic CAD compared to women even at younger ages. More critical CAD including LM disease and three-vessel disease were also more prevalent in men. We need to understand this observed sex differences, which could apply in the clinical evaluation and management of patients with suspected CAD. Specifically, since men are more likely to have severe CAD, it is desirable to recommend more active tests and intensified management to men with suspected CAD.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13293-021-00411-1>.

Additional file 1. Table S1. Multiple binary logistic regression analyses showing independent predictors for LM disease and three vessel disease.

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Authors' contributions

H-LK and M-AK designed the research. H-LK wrote the manuscript. H-JK, MK, SMP, HJY, YSB, SMP, MSS and KSH were involved in literature searches and manuscript editing. M-AK revised the manuscript and had all responsibility of this study. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol complied with the Declaration of Helsinki, and was approved by the Institutional Review Board of each participating hospital. Written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests.

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