ORIGINAL ARTICLE

Comparison of clinical characteristics, in-hospital course, and 12-month prognosis in women and men with chronic coronary syndromes

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KEY WORDS
chronic coronary syndromes, comparison, men, prognosis, women

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ABSTRACT

BACKGROUND The prognosis of men and women with chronic coronary syndromes (CCS) remains ambiguous.

AIMS This study aimed to compare the clinical characteristics and 12-month prognosis of women and men with CCS included in the prospective single-center registry.

METHODS The study was based on the Prospective Registry of Stable Angina Management and Treatment (PRESAGE) including 11 021 patients with CCS hospitalized between 2006 and 2016 and subjected to coronary angiography. The composite endpoint included all-cause death, nonfatal myocardial infarction, acute coronary syndrome with revascularization, unstable coronary artery disease, or stroke.

RESULTS Women were older than men (mean [SD] age, 66.6 [9] vs 63.5 [9.6] years; P <0.001). Arterial hypertension (85.8% vs 79%; P <0.001) and type 2 diabetes (38.2% vs 33.7%; P <0.001) were more often diagnosed in women compared with men. Multivessel disease or left main disease were more frequent in men. Percutaneous coronary intervention and coronary artery bypass grafting were more often performed in men than in women (47.1% vs 36%, P <0.001 and 10.6% vs 6.1%, P <0.001, respectively). At 12-month follow-up, the composite endpoint was more frequently reached in men (7.4% vs 10.2%; P <0.001), including death (3.3% vs 4.5%; P = 0.002). In multivariable analysis, sex was not an independent predictor of the composite endpoint (hazard ratio, 1.08; 95% CI, 0.89–1.31, P = 0.45).

CONCLUSIONS Women and men with CCS differ in terms of the incidence of risk factors and revascularization treatments received. In men, a higher frequency of death and the composite endpoint was noted at 12-month follow-up. However, sex was not an independent predictor of patient outcomes at 12 months.

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INTRODUCTION The prognosis of women and men with chronic coronary syndromes (CCS) remains ambiguous in the light of the available data. There are few studies focusing on the differences in long-term prognosis between men and women with coronary artery disease (CAD) and the results of those analyses are often inconclusive.[1-3] Therefore, the aim of our study was to compare clinical characteristics, in-hospital complications, and 12-month prognosis in women and men with CCS included in the prospective single-center registry.

METHODS **Registry design and study population** The Prospective Registry of Stable Angina Management and Treatment (PRESAGE), maintained by 3rd Department of Cardiology,

WHAT'S NEW?

The Prospective Registry of Stable Angina Management and Treatment (PRESAGE) includes patients diagnosed with chronic coronary syndromes and subjected to coronary angiography during hospitalization. Our registry-based study showed that men and women represent heterogenous groups with varied clinical characteristics. What is more, sex was not an independent predictor of 12-month outcomes in multivariable analysis.

Medical University of Silesia, Silesian Center for Heart Diseases in Zabrze, Poland, includes patients diagnosed with CCS who underwent coronary angiography during hospitalization.

The diagnosis of CCS was established based on the current guidelines of the European Society of Cardiology.[4] Patients with vasospastic and/or microvascular angina were additionally entered in the registry. Patients presenting to our center several times were assessed as a single patient (data from the first hospitalization were included). The study was approved by an appropriate institutional review board. Patient consent to participate in the study was not required.

Women and men were compared in terms of clinical characteristics, angiographic findings, revascularization, in-hospital complications, and pharmacological recommendations at discharge from the hospital. The comparison of 12-month prognosis was based on the assessment of the incidence of a composite endpoint that consisted of all-cause death, nonfatal myocardial infarction (MI), acute coronary syndrome (ACS)–driven revascularization, unstable angina, or stroke. Independent factors influencing the occurrence of a composite endpoint during the 12-month follow-up were evaluated in a multivariable analysis. Data concerning the 12-month follow-up were obtained from the Polish National Health Fund (Polish, Narodowy Fundusz Zdrowia). Due to the preliminary assumptions of our analysis, we decided to follow up the study population for 12 months. There was no difference in the duration of follow-up between women and men.

Definitions Myocardial infarction was diagnosed in accordance with the current guidelines of the European Society of Cardiology.[5,6] Acute coronary syndrome–driven revascularization was defined as acute myocardial ischemia requiring urgent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Unstable angina was diagnosed in the case of an acute myocardial ischemia episode manifested by acute ischemic changes on electrocardiography, with no biomarkers of myocardial injury present. Stroke was regarded as acute ischemia or bleeding into the central nervous system. The diagnosis of hypertension was established when repeated arterial pressure values of at least 140/90 mm Hg were noted or the patient used hypotensive drugs. Type 2 diabetes was diagnosed when the level of fasting glucose was 2-fold higher than 125 mg/dl or the level of casual plasma glucose exceeded 200 mg/dl, or the patient had already been using antidiabetic drugs or insulin. Hypercholesterolemia was identified when total cholesterol levels exceeded 200 mg/dl and/or low-density lipoprotein cholesterol levels were above 130 mg/dl, or lower values were achieved using statins. Obesity was diagnosed when the body mass index exceeded 30 kg/m^2. A positive family history of premature CAD was regarded as the occurrence of CAD under 50 years of age in men and under 60 years of age in women. Significant CAD was diagnosed in the presence of 70% stenosis or greater in an artery with a reference diameter of more than 2 mm or in the presence of 50% stenosis or greater in the left main coronary artery or left anterior descending artery. Bleeding during hospitalization was considered significant if hemoglobin levels dropped below 5 g/dl and/or hematocrit levels decreased by more than 15%, leading to hemorrhagic shock and/or condition requiring blood transfusion.

Statistical analysis Statistical analysis included descriptive statistics of baseline characteristics, angiographic findings, management, in-hospital events as well as the occurrence and predictors of adverse events during the 12-month follow-up. Continuous variables were expressed as mean (SD) for data following normal distribution or median (interquartile range [IQR]) for data demonstrating non-normal distribution. Continuous variables with normal distribution were compared using the *t* test, and others, using the Mann–Whitney test. The normality of distribution was verified with the Shapiro–Wilk test. Categorical variables were summarized in frequency tables and compared using the Pearson χ^2 test, also with the Yates correction if the expected number of observations was less than 5. Twelve-month outcomes were expressed using Kaplan–Meyer curves and the log-rank test. The effects of the evaluated parameters on the 12-month incidence of a composite endpoint was assessed using multivariable Cox proportional hazard regression models, with results expressed as hazard ratios and 95% CIs. Candidate variables were entered into the model, including parameters with a significant influence on univariate analysis: age, atrial fibrillation, body mass index, chronic obstructive pulmonary disease (COPD), current smoking status, diabetes, male sex, glucose levels on admission, hemoglobin levels on admission, heart rate on admission, lack of chest pain on admission, left bundle branch block on admission, left main CAD, left ventricular ejection fraction (LVEF), significant CAD, multivessel CAD, New York Heart Association (NYHA) class III, NYHA class IV, peripheral artery disease, prior myocardial infarction,

prior revascularization, prior stroke, revascularization during hospitalization, serum creatinine levels on admission, and white blood cell count on admission. Second, after univariate Cox proportional hazard regression, a correlation analysis was performed to eliminate linearly dependent factors (absolute value, r >0.5). We used the backward stepwise regression method with the significance level set at P <0.1 for the variables remaining in the model, provided that the variable "sex" remained in the model regardless of the P value. As sex was the subject of this analysis, we decided that this variable will be most appropriate. For all analyses, a 2-tailed P value less than or equal to 0.05 was considered significant. The Statistica 13 software (StatSoft, Inc., Tulsa, Oklahoma, United States) was used for all calculations.

TABLE 1 **Baseline demographic and clinical characteristics of the study patients**

Characteristics	Total population (n = 11 021)	Women (n = 3858)	Men (n = 7163)	*P* value
Age, y, mean (SD)	64.6 (9.5)	66.6 (9)	63.5 (9.6)	<0.001
Prior MI	4016 (37.3)	1001 (26.7)	3015 (43.1)	<0.001
Non-STEMI	1063 (9.9)	311 (8.3)	752 (10.7)	<0.001
STEMI	2678 (24.9)	654 (17.4)	2024 (28.9)	<0.001
Prior PCI	3806 (35.4)	1043 (27.8)	2763 (39.5)	<0.001
Prior CABG	1284 (11.9)	280 (7.5)	1004 (14.3)	<0.001
Prior stroke	614 (5.7)	197 (5.2)	417 (5.9)	0.14
Peripheral artery disease	1597 (14.9)	503 (13.5)	1094 (15.7)	0.003
Atrial fibrillation	1905 (17.7)	642 (17.1)	1263 (18)	0.26
Arterial hypertension	8888 (81.3)	3282 (85.8)	5606 (79)	<0.001
Family history of premature CAD	2137 (20.2)	883 (23.9)	1254 (18.3)	<0.001
Diabetes	3800 (35.3)	1434 (38.2)	2366 (33.7)	<0.001
Hypercholesterolemia	8177 (75.6)	2877 (76)	5300 (75.4)	0.49
History of smoking	5048 (46.9)	1246 (33.2)	3802 (54.2)	<0.001
Current smoking status	2447 (22.7)	626 (16.7)	1821 (26)	<0.001
COPD	665 (6.2)	169 (4.5)	496 (7.1)	<0.001
CCS class I	4358 (41.7)	1621 (44.3)	2737 (40.3)	<0.001
CCS class II	3679 (35.2)	1211 (33.1)	2468 (36.3)	<0.001
CCS class III	2456 (23.5)	827 (22.6)	1629 (24)	0.12
NYHA class I	6156 (57.6)	1998 (53.5)	4158 (59.8)	<0.001
NYHA class II	3117 (29.1)	1197 (32)	1920 (27.6)	<0.001
NYHA class III	1302 (12.2)	506 (13.6)	796 (11.4)	0.002
NYHA class IV	111 (1)	34 (0.9)	77 (1.1)	0.34
LVEF, %, mean (SD)	47.1 (11)	50 (8.8)	45.3 (11.6)	<0.001
LVEF <35%	1 159 (12.5)	177 (5.6)	982 (16)	<0.001
BMI, kg/m^2, median (IQR)	28 (26–31)	29 (25–32)	28 (26–31)	<0.001
Serum creatinine, µmol/l, median (IQR)	80 (68–95)	70 (60–83)	84 (73–99)	<0.001
GFR, ml/min/1.73 m^2, median (IQR)	82 (67–97)	78 (63–93)	84 (69–99)	<0.001
GFR <60 ml/min/1.73 m^2	1768 (16.1)	781 (20.3)	987 (13.8)	<0.001
Hemoglobin, g/l, median (IQR)	8.8 (8.2–9.3)	8.4 (7.9–8.8)	9 (8.4–9.5)	<0.001
White blood cells, × 10^3/µl, median (IQR)	7 (5.9–8.4)	6.8 (5.7–8.4)	7.1 (6–8.4)	<0.001

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

TABLE 2 Angiographic characteristics of the study population

Characteristics	Total population (n = 11 021)	Women (n = 3858)	Men (n = 7163)	*P* value
CAD				
Nonobstructive CAD	33 (3.6)	47 (1.8)	25 (1.8)	<0.001
Single-vessel CAD	3314 (30.1)	1014 (26.3)	2300 (32.1)	<0.001
Multivessel CAD	4071 (36.9)	1031 (26.7)	3040 (42.4)	<0.001
Left main CAD	668 (6.1)	141 (3.7)	527 (7.4)	<0.001
Chronic total occlusion	3077 (27.9)	683 (17.7)	2394 (33.4)	<0.001
Diagnostic workup				
Bypass angioography	1284 (11.6)	280 (7.3)	1004 (14)	<0.001
Fractional flow reserve assessment	401 (3.6)	133 (3.5)	268 (3.7)	0.43
Intravascular ultrasound	107 (1)	36 (0.9)	71 (1)	0.77
Interventional treatment				
PCI	4765 (43.2)	1388 (36)	3377 (47.1)	<0.001
PCI during index hospitalization	4743 (43)	1381 (35.8)	3362 (46.9)	<0.001
PCI during next hospitalizations	709 (6.4)	205 (5.3)	504 (7)	<0.001
Stent implantation	4227 (38.4)	1246 (32.3)	2981 (41.6)	<0.001
Bare-metal stent implantation	1210 (11)	354 (9.2)	856 (12)	<0.001
Drug-eluting stent implantation	3078 (27.9)	913 (23.7)	2165 (30.2)	<0.001
Drug-eluting balloon	86 (0.8)	17 (0.4)	69 (1)	0.003
CABG	997 (9)	236 (6.1)	761 (10.6)	<0.001

Data are presented as number (percentage) of patients.

Abbreviations: see TABLE 1

TABLE 3 Pharmacotherapy of the study population

Drug	Total population (n = 11 021)	Women (n = 3858)	Men (n = 7163)	*P* value
Acetylsalicylic acid	8767 (90)	2 923 (88.3)	5 844 (90.7)	<0.001
P2Y12 receptor inhibitor	4847 (49.7)	1394 (42.1)	3453 (53.6)	<0.001
Oral anticoagulant	1621 (16.6)	495 (15)	1126 (17.5)	0.002
Nitrate	39 954 (40.5)	1384 (41.8)	2570 (39.9)	0.07
β-Blocker	9103 (93.3)	3092 (93.4)	6011 (93.3)	0.8
ACEI / ARB	8528 (87.4)	2848 (86)	5680 (88.1)	0.003
Calcium antagonist	2377 (24.9)	997 (30.7)	1 380 (21.9)	<0.001
Aldosterone antagonist	3234 (33.8)	979 (30.2)	2255 (35.7)	<0.001
Statin	8598 (89.2)	2879 (87.9)	5719 (89.9)	0.003
Fibrate	392 (4.1)	93 (2.8)	299 (4.7)	<0.001
Ezetimibe	44 (0.5)	17 (0.5)	27 (0.4)	0.51
Diuretic	4734 (48.5)	1586 (47.9)	3148 (48.9)	0.38
Proton pump inhibitors	4490 (46)	1476 (44.6)	3014 (46.8)	0.04
Digoxin	388 (4.1)	99 (3.1)	289 (4.6)	<0.001
Trimetazidine	697 (7.3)	356 (11)	341 (5.4)	<0.001
Ivabradine	58 (0.6)	14 (0.4)	44 (0.7)	0.11
Oral antidiabetic	1791 (18.7)	682 (21)	1109 (17.6)	<0.001
Insulin	1182 (12.4)	469 (14.5)	713 (11.3)	<0.001

Data are presented as number (percentage) of patients.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

TABLE 4 In-hospital as well as mid- and long-term outcomes of the study population

Outcome	Total population (n = 11 021)	Women (n = 3858)	Men (n = 7163)	*P* value
In-hospital complications				
Any	164 (1.5)	70 (1.8)	94 (1.3)	0.04
Death	47 (0.4)	17 (0.4)	30 (0.4)	0.87
MI	28 (0.3)	10 (0.3)	18 (0.3)	0.94
Target vessel revascularization	14 (0.1)	6 (0.2)	8 (0.1)	0.54
Stroke	6 (0.1)	2 (0.1)	4 (0.1)	0.93
Major bleeding	63 (0.6)	33 (0.9)	30 (0.4)	0.004
Cardiac arrest	74 (0.7)	27 (0.7)	47 (0.7)	0.86
6-month major adverse cardiovascular events				
Any	535 (4.9)	151 (3.9)	384 (5.4)	<0.001
Death	285 (2.6)	83 (2.2)	202 (2.8)	0.04
MI	167 (1.5)	47 (1.2)	120 (1.7)	0.06
Unstable angina	219 (2)	71 (1.8)	148 (2.1)	0.41
ACS-driven revascularization	161 (1.5)	44 (1.1)	117 (1.6)	0.04
Stroke	46 (0.4)	10 (0.3)	36 (0.5)	0.06
1-year composite endpoint				
Any	1018 (9.2)	287 (7.4)	731 (10.2)	<0.001
Death	449 (4.1)	126 (3.3)	323 (4.5)	0.002
MI	245 (2.2)	67 (1.7)	178 (2.5)	0.011
Unstable angina	342 (3.1)	101 (2.6)	241 (3.4)	0.031
ACS-driven revascularization	270 (2.4)	68 (1.8)	202 (2.8)	<0.001
Stroke	97 (0.9)	25 (0.6)	72 (1)	0.06

Data are presented as number (percentage) of patients.

Abbreviations: ACS, acute coronary syndrome; others, see TABLE 1

RESULTS Between January 1, 2006 and December 31, 2016, a total of 13 052 patients with confirmed CAD were entered into the PRESAGE. After the exclusion of patients with a significant valvular defect and active malignancy, 11 021 patients were included for further analysis. Patients were divided by sex into 2 groups: women (3858 [35%]) and men (7163 [65%]). The comparative analysis of clinical and angiographic characteristics of both groups is shown in TABLE 1. Data on the used pharmacotherapy are presented in TABLE 2, and in-hospital and long-term treatment results of both study groups, in TABLE 3. Except the higher frequency of significant bleeding in women, no differences in the frequency of deaths and complications were observed between the 2 groups during hospitalization (TABLE 4).

Independent risk factors, identified in multivariable analysis and affecting the occurrence of the composite endpoint within 12 months, included: serum creatinine levels, age, white blood cell count, LVEF, prior myocardial infarction, hemoglobin levels on admission, NYHA class III, left main CAD, peripheral artery disease, COPD, significant CAD, and NYHA class IV. Sex was not an independent predictor of 12-month outcomes (FIGURES 1 and 2) (hazard ratio, 1.08; 95% CI, 0.89–1.131; $P = 0.45$). The Kaplan–Meier curves for 12-month outcomes are presented in FIGURE 3.

DISCUSSION Few studies have compared CCS and previously stable CAD in women and men.[7-9] The available reports based on registries of treatment records of patients with stable CAD show that women constitute a minority: (CLARIFY [The Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease], 22.6%; PCI registry of the German Cardiac Society, 34.6%; and PRESAGE, 35%).[2,10] Women included in CAD registries were older than men. However, the mean (SD) age of women compared with that of men was relatively young in both CLARIFY and PRESAGE registries (66.6 [10] vs 63.4 [10.5] years and 66.6 [9] vs 63.5 [9.6] years, respectively). According to some studies, the risk of CAD in women seems to be underestimated,[11] probably also owing to additional premenopausal risk factors such as pregnancy-related hypertension or polycystic

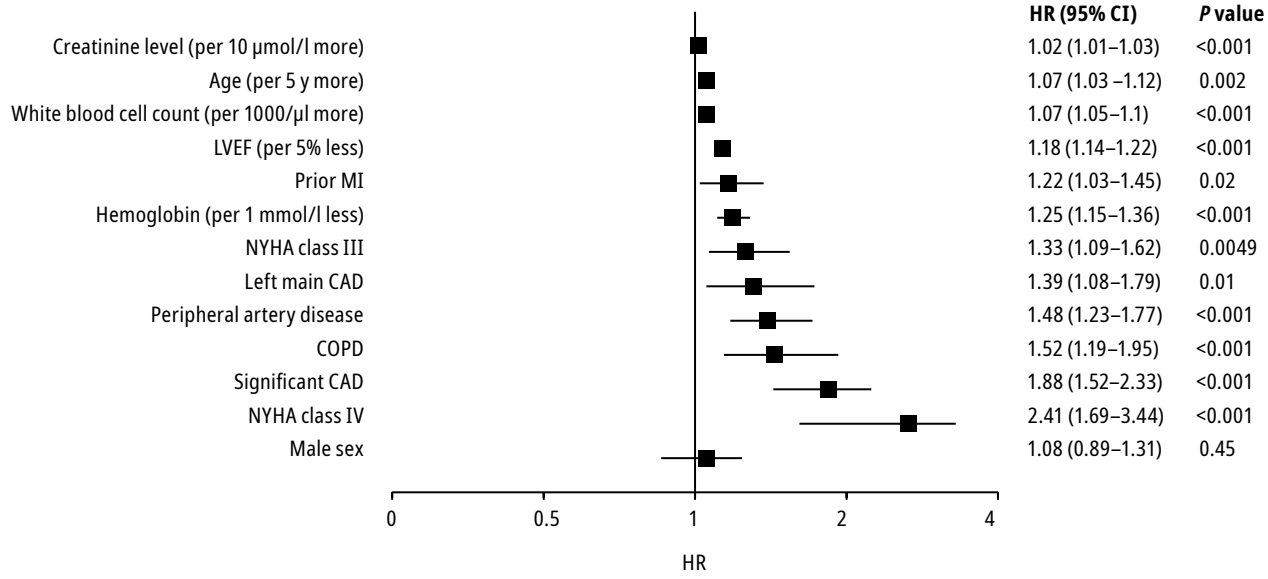

FIGURE 1 Multivariable analysis of independent risk factors for the composite endpoint at 12 months
Abbreviations: HR, hazard ratio; others, see TABLE 1

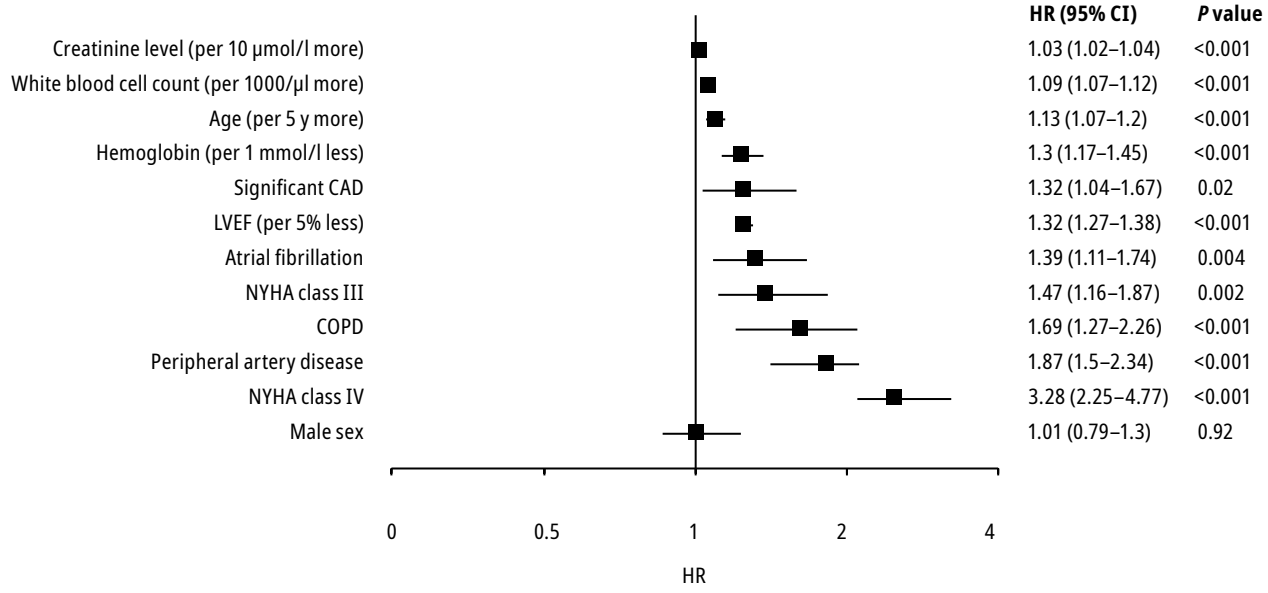

FIGURE 2 Multivariable analysis of independent risk factors for mortality at 12 months
Abbreviations: see TABLE 1 and FIGURE 1

ovary syndrome.[12-14] The results of a comparative analysis of clinical characteristics included in the CLARIFY and PRESAGE registry are consistent. Men more often than women had MI and underwent coronary artery interventions (PCI or CABG). As a result, men were more frequently diagnosed with heart failure with reduced ejection fraction (LVEF <35%) than women. In our registry, 12.5% of patients presented with LVEF below 35%, which means that one-eighth of patients suffered from heart failure. Moreover, COPD, current smoking status, and peripheral artery disease were also more frequently noted in men. As opposed to men, the main risk factors and comorbidities in women included type 2 diabetes, hypertension, and chronic kidney disease. Considering the results of coronary angiography from our registry, nonsignificant lesions in coronary arteries were more frequently observed in women. Merz et al[12] showed that women are more likely to suffer from microcirculatory and endothelial dysfunction, vasospasms, or spontaneous dissections within the coronary arteries. The men included in the PRESAGE, similar to those in the Euro Heart Survey, were characterized by more advanced coronary artery disease than women.[8-10] The men included in the PRESAGE, similar to other studies, were more often

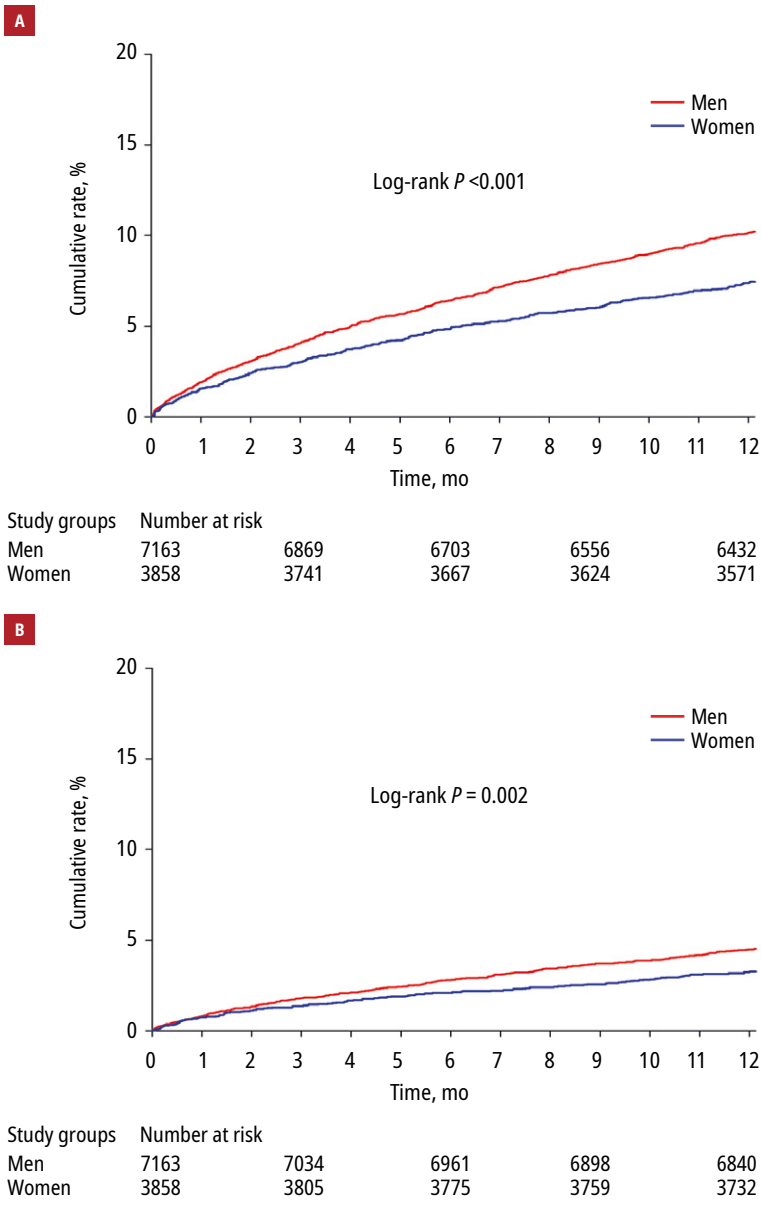

FIGURE 3 Kaplan–Meyer curves for the composite endpoint (**A**) and mortality (**B**) in women and men with chronic coronary syndromes at 12 months

deemed eligible for revascularization procedures than women.[9,15,16]

There are few studies analyzing in-hospital complications in CCS.[15] Similar to our analysis, the SAFE-PCI (Study of Access Site for Enhacement of PCI for Women) study showed that women more often required blood transfusions because of perioperative bleeding.[15]

Our study showed no differences in the frequency of use of β-blockers, aspirin, and P2Y12 receptor inhibitors in the study groups. The analysis of pharmacotherapy demonstrated that almost 50% of patients received diuretics and almost 30%, aldosterone antagonists. Men more often received angiotensin-converting enzyme inhibitors and statins. Also, the pharmacotherapy analysis in the CLARIFY study showed that women with CCS received less optimal treatment than men.[7]

Long-term prognosis of men and women with CCS remains unclear. In the CLARIFY registry, despite significant differences in clinical characteristics, results of coronary angiography, and revascularization treatment (PCI or CABG), the 12-month prognosis did not differ between particular groups.[2] There were no differences in the frequency of deaths, MI, unstable angina, or composite endpoints in women and men.[2] The authors emphasized that only a small percentage of women in their study were deemed eligible for and subjected to coronary angiography and PCI, despite a higher number of risk factors and comorbidities.[8] Some studies suggested worse prognosis in women undergoing PCI, as the risk of restenosis in the implanted stent is higher in vessels of a smaller diameter, which are actually more common in women.[8] In the Euro Heart Survey of women with angiographically confirmed CAD, death, MI, or sudden cardiac death were twice as frequent as in men during the 12-month follow-up. In that study, the female sex proved to be an independent risk factor for cardiovascular events only in patients with angiographically confirmed CAD.[8] In our study, the prognosis for men differed from that for women. Apart from being younger, men presented significant risk factors that worsen long-term prognosis. We observed that the percentage of composite endpoints, including all-cause deaths, was higher in men at 12 months. Significant lesions in coronary arteries, left main CAD, COPD, prior MI, and NYHA class III and IV were identified as independent risk factors in multivariable analysis.

Limitations Our analysis was based on the data of patients treated in a single, high-volume reference center, which, however, has advanced diagnostic and treatment facilities.

Conclusions Women and men with CCS differ in terms of the incidence of risk factors, history of MI, and revascularization treatments. Men were found to have a higher frequency of deaths and composite endpoints during the 12-month follow-up. However, in multivariable analysis, sex was not identified as an independent factor regarding the occurrence of the composite endpoint and death during long-term follow-up.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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