International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Gender differences in long-term clinical outcomes and prognostic factors in patients with vasospastic angina

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ARTICLE INFO

Article history:
Received 19 December 2016
Received in revised form 19 April 2017
Accepted 23 May 2017
Available online xxxx

Keywords:
Gender difference
Prognosis
Vasospastic angina

ABSTRACT

Background: Men are more likely to suffer from vasospastic angina (VSA) than women; however, gender differences in the long-term prognosis of VSA patients have not been fully elucidated. We sought to investigate clinical outcomes and predictive factors of VSA patients according to gender.
Methods: A total of 986 patients (838 men and 148 women) with a positive result on intracoronary ergonovine provocation test between January 2003 and December 2014 were analyzed. The primary outcome was major adverse cardiac events (MACE), defined as a composite of cardiac death, acute myocardial infarction, revascularization, or rehospitalization due to recurrent angina.
Results: Women were younger and showed a lower prevalence of smoking or fixed coronary stenosis than men. The risk for MACE was similar between male and female patients (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.65–1.39; p = 0.79). In multivariable prediction models for MACE, high-sensitivity C-reactive protein (hs-CRP) level was a significant predictor of MACE in male patients (HR, 1.95; 95% CI, 1.25–3.06; p = 0.003), but there was no significant predictor in female patients. There was a significant interaction between hs-CRP level and MACE rate across genders (interaction p = 0.02).
Conclusions: Long-term clinical outcome was not different between genders. Hs-CRP was an important predictor of long-term clinical outcomes in male patients with VSA, but not in female patients.

1. Introduction

Gender differences in the manifestation and clinical outcomes of patients with ischemic heart disease have been clearly demonstrated. Although the prevalence of ischemic heart disease is much lower in women than in men, female patients have paradoxically shown a worse long-term prognosis than male patients [1]. In recent studies these gender differences were explained by functional abnormalities of the coronary artery including abnormal coronary reactivity and microvascular dysfunction [2,3].

Coronary artery spasm is characterized by transient myocardial ischemia due to abnormal coronary artery hyper-reactivity and is an important pathophysiology in a wide variety of ischemic heart diseases [4]. The prevalence of vasospastic angina (VSA) was repeatedly reported to be higher in men than in women and its clinical characteristics were also shown to vary according to gender [5,6]. However, a gender difference in the prognosis of VSA has not been fully investigated [7]; in particular, gender-specific prognostic predictors remain to be elucidated. Therefore, we sought to investigate gender differences in long-term prognosis and to determine gender-specific prognostic factors in VSA patients.

2. Methods

2.1. Study population

A total of 1198 consecutive patients with positive results on ergonovine provocation test were enrolled from January 2003 to December 2014 at Samsung Medical Center (Fig. 1). We excluded 173 patients with >70% diameter coronary artery stenosis of major (≥2.5 mm) epicardial coronary arteries via visual estimation on angiography and 39 patients who refused follow-up. Finally, 986 patients (838 men and 148 women) were analyzed in this study. The Samsung Medical Center Institutional Review Board approved this study and waived the requirement for written informed consent for access to an institutional registry.

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http://dx.doi.org/10.1016/j.ijcard.2017.05.094
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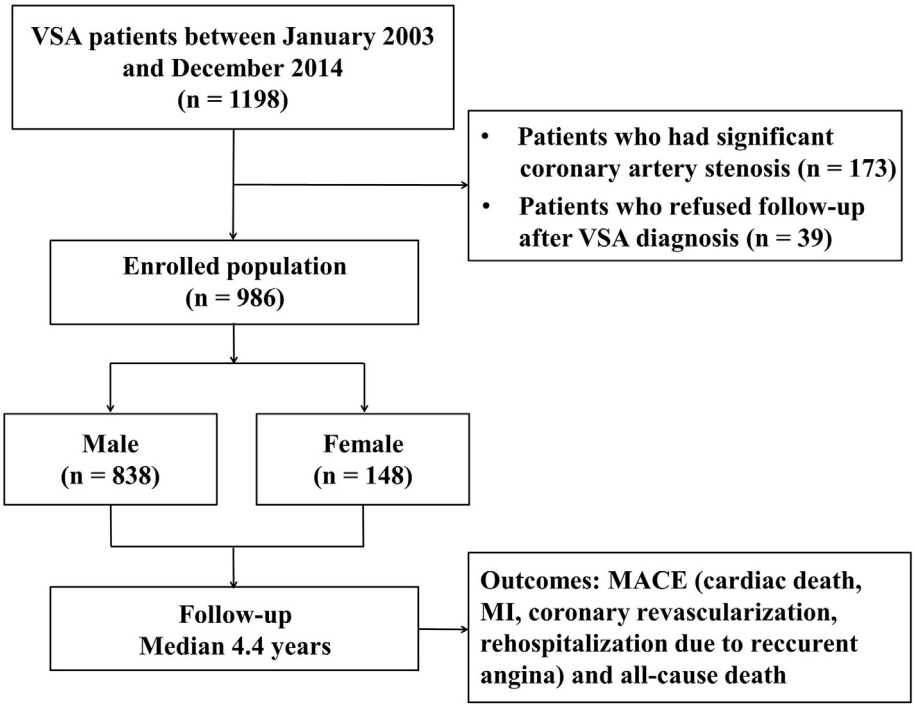

Fig. 1. Flow chart of study subjects. MACE, major adverse cardiac events; MI, myocardial infarction; VSA, vasospastic angina.

2.2. Coronary angiography and provocation test for VSA

All vasoactive medication that could have an influence on vascular reactivity was withheld for at least 48 h before the provocation test, and blood sampling was done at the first day of index hospitalization. Spasm provocation test was performed with intracoronary ergonovine injection after baseline coronary angiography. Incremental doses of 20 (E1), 40 (E2), and 80 (E3) μg ergonovine were injected into the left coronary artery. If coronary spasm was not induced in the left coronary artery, incremental doses of 10 (E1), and 20 (E2) μg were injected into the right coronary artery. Once spasm was provoked, intracoronary nitroglycerin was immediately infused. Positive provocation result was defined as subtotal (>90% diameter stenosis) or total occlusion provocation on angiography after ergonovine intracoronary injection, accompanied by chest pain or electrocardiography (ECG) change [8]. Spontaneous total or subtotal spasm on baseline coronary angiography that was resolved by intracoronary nitroglycerin was also defined as a positive result. ECG change was defined as ST-segment elevation, depression (≥0.1 mV), or T-wave inversion in at least two consecutive leads. A multivessel spasm was defined as a positive spasm in 2 or more major epicardial coronary arteries, and a diffuse spasm was defined as a positive spasm in 2 or more segments of coronary artery.

2.3. Study outcomes

The primary outcome was major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction, revascularization, and rehospitalization due to recurrent angina. Secondary outcomes were individual components of MACE and all-cause death. All deaths were considered to be cardiac unless a definite non-cardiac cause could be established. Myocardial infarction was defined as elevation of cardiac biomarkers above the 99th percentile upper reference limit accompanied by at least one of the following: typical angina symptoms, ischemic ST-T change, pathologic Q wave, new-onset left bundle branch block in ECG, new loss of viable myocardium, new regional wall motion abnormality on image modality, and identification of a thrombus on coronary angiography [9]. Revascularization was defined as recanalization of epicardial coronary artery by percutaneous coronary intervention or bypass graft surgery. Rehospitalization was defined as any hospitalization after the index hospital discharge due to recurrent angina symptoms of typical chest pain, atypical chest pain, dyspnea, syncope or dizziness, palpitation, or aborted cardiac arrest.

2.4. Statistical analysis

Continuous variables were expressed as medians (25th–75th percentiles) and compared using an independent *t*-test or the Mann-Whitney test as appropriate. Categorical variables were expressed as numbers with percentages and compared using chi-square test or Fisher's exact test as appropriate. Event-free survival was analyzed by the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard models were used to compare the risk of adverse events between male and female groups. To determine gender-specific prognostic predictors, we applied multivariable Cox proportional hazard models in each gender group. Proportional hazard assumption was

Table 1
Baseline characteristics of patients with vasospastic angina.

	All (n = 986)	Male (n = 838)	Female (n = 148)	p value
Age, years	56 (49–63)	57 (50–63)	53 (48–62)	0.03
Body mass index, kg/m^2	24.4 (22.6–26.0)	24.4 (22.7–26.0)	24.0 (21.9–26.0)	0.13
Coronary risk factors				
Diabetes mellitus	230 (23.3)	200 (23.9)	30 (20.3)	0.34
Hypertension	383 (38.8)	322 (38.4)	61 (41.2)	0.52
Current smoking	279 (28.3)	272 (32.5)	7 (4.7)	<0.001
Dyslipidemia	203 (20.6)	169 (20.2)	34 (23.0)	0.44
Prior myocardial infarction	32 (3.2)	28 (3.3)	4 (2.7)	0.68
Circadian pattern of angina				0.007
Night to morning	338 (38.8)	309 (36.9)	74 (50.0)	
Daytime	331 (33.6)	294 (35.1)	37 (25.0)	
Other	272 (27.6)	235 (27.6)	37 (25.0)	
Clinical presentation				
Resting angina	854 (86.6)	722 (86.2)	132 (89.2)	0.32
Myocardial infarction	37 (3.8)	32 (3.8)	5 (3.4)	0.80
ST elevation during spontaneous attack	14 (1.4)	14 (1.6)	0 (0.0)	0.25
Cardiac arrest	36 (3.7)	34 (4.1)	2 (1.4)	0.11
Laboratory findings				
LVEF, %	65 (60–68)	64 (60–68)	65 (62–69)	0.08
Hemoglobin, g/dl	14.5 (13.6–15.5)	14.8 (14.0–15.6)	13.0 (12.4–13.8)	<0.001
Creatinine, mg/dl	0.91 (0.78–1.02)	0.94 (0.84–1.04)	0.69 (0.61–0.76)	<0.001
Total cholesterol, mg/dl	169 (146–193)	168 (146–193)	176 (152–197)	0.045
Triglyceride, mg/dl	128 (89–193)	133 (93–199)	105 (75–155)	<0.001
HDL cholesterol, mg/dl	46 (38–54)	45 (38–53)	50 (42–58)	<0.001
LDL cholesterol, mg/dl	103 (83–125)	102 (82–124)	108 (84–129)	0.15
Hs-CRP, mg/dl	0.08 (0.04–0.19)	0.08 (0.04–0.20)	0.06 (0.03–0.16)	0.12

Values are presented as median (25th–75th percentile) or number of patients (%).
HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

Please cite this article as: D.H. Lee, et al., Gender differences in long-term clinical outcomes and prognostic factors in patients with vasospastic angina, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.05.094