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Gender differences in major adverse cardiovascular outcomes among aged over 60 year-old patients with atherosclerotic cardiovascular disease

A population-based longitudinal study in Taiwan

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Abstract

Atherosclerotic cardiovascular disease (ASCVD) including cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD), contributes to the major causes of death in the world. Although several studies have evaluated the association between gender and major adverse cardiovascular outcomes in old ASCVD patients, the result is not consistent. Hence, we need a large-scale study to address this issue.

This retrospective cohort study included aged over 60 year-old patients with a diagnosis of ASCVD, including CVD, CAD, or PAD, from the database contained in the Taiwan National Health Insurance Bureau during 2001 to 2004. The matched cohort was matched by age, comorbidities, and medical therapies at a 1:1 ratio. A total of 9696 patients were enrolled in this study, that is, there were 4848 and 4848 patients in the matched male and female groups, respectively. The study endpoints included acute myocardial infarction, hemorrhagic stroke, ischemic stroke, vascular procedures, in-hospital mortality, and so on. In multivariate Cox regression analysis in matched cohort, the adjusted hazard ratios (HRs) for female group in predicting acute myocardial infarction, hemorrhagic stroke, ischemic stroke, vascular procedures, and in-hospital mortality were 0.67 ($P < .001$), 0.73 ($P = .0015$), 0.78 ($P < .001$), 0.59 ($P < .001$), and 0.77 ($P = .0007$), respectively.

In this population-based propensity matched cohort study, age over 60 year-old female patients with ASCVD were associated with lower rates of acute myocardial infarction, hemorrhagic stroke, ischemic stroke, vascular procedures, and in-hospital mortality than male patients. Further prospective studies may be investigated in Taiwan.

Abbreviations: ACS = acute coronary syndrome, AMI = acute myocardial infarction, ASCVD = atherosclerotic cardiovascular disease, CAD = coronary artery disease, CVD = cerebrovascular disease, PAD = peripheral arterial disease.

Keywords: atherothrombosis, cerebrovascular disease, coronary artery disease, gender, peripheral artery disease, Taiwan, women

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

The elderly population is rapidly growing in worldwide.[1] Burden of atherosclerotic cardiovascular disease (ASCVD) including cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD), increased with age and contributed to the leading causes of death and lots of challenge on healthcare.[1–4] In previous epidemiological studies, 45% to 63% of patients with age over 60 years old had either CVD, CAD, or PAD.[5,6]

Pharmacologic therapies for ASCVD including antiplatelet agents, angiotensin-converting enzyme inhibitors, ß blockers and lipid-lowing agents are the same between young and old patients.[7–10] Furthermore, clinical guidelines for evaluation and treatment of acute coronary syndrome, acute stroke, and PAD, are the same between men and women.[11–13] However, the gender difference in clinically presentation, treatment, and prognosis for ASCVD are currently under attention and investigation.[14–18] In fact, the clinical characteristics and outcomes from those studies are inconsistent. Women with CAD and CVA are typically senior and have more comorbidities and risk factors such as hypertension and diabetes than men.[14–18] Fewer studies are available about cardiovascular outcome difference in gender in patients with PAD.

Although several studies performed in western countries showed the gender difference in the management strategy and cardiovascular outcome in old patients with ASCVD, there was no large-scale study to evaluate the relationship between gender and adverse cardiovascular events in old patients with ASCVD in Asian countries.[19,20] Therefore, we conducted this large study to assess the relationship between gender and adverse cardiovascular outcomes in aged patients with full spectrum of atherothrombotic diseases in Taiwan.

2. Methods

2.1. Ethics statement

The retrospective study protocol was approved by the institutional review board of the Kaohsiung Medical University Hospital. Because patient records and information were anonymized and de-identified prior to analysis, the written informed patient consent was waived by the IRB.

2.2. Data source and study sample

We analyzed the database of 1,000,000 random subjects from the National Health Insurance Research Dataset provide by the National Health Research Institute (Registered number 98178).[21] This study population consisted of all patients with more than 2 outpatient or inpatient claims with a diagnosis of ASCVD, including CVD, CAD, or PAD between July 1, 2001 and December 31, 2004. Initially, these patients with CVD, CAD, or PAD were enrolled by their disease code of international classification of diseases 9th revision clinical modification (ICD-9-CM) or their related vascular procedure codes of ICD-9-CM during study period.[21–23] The data of the first claim with a CVD, CAD, or PAD diagnosis was considered the index date. The patients who were younger than 60 years old and had a diagnosis of CVD, CAD, or PAD before index date were excluded.[24] Finally, these patients with newly diagnosed CVD, CAD, or PAD who received any antithrombotic or antiplatelet agents, such as aspirin, clopidogrel, ticlopidine, warfarin, or cilostazol, ≧30 days after each patient's index date were finally identified to form our study patients.[21] Baseline characteristics including age, sex, treatment information, and comorbidities were extracted from all claims within 180 days before the index data. Detail description of baseline comorbidity, social economic and geographic data were published in our previous study.[21]

Medical treatments and comorbidities play an important role in cardiovascular outcomes between male and female patients with ASCVD. We strictly designed a matched cohort. In this matched cohort, the age, comorbidities, and medical treatments were comparable between male and female groups. The comorbidities and medical treatments were included DM, hypertension, hyperlipidemia, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, aortic and mitral valve stenosis, peptic ulcer disease, using of anti-thrombotic agents, using of anti-hypertensive agents, using of anti-diabetic agents, using of lipid-lowing agents, and using of proton pump inhibitors. Patients were excluded from the matched cohort analysis if no match was found. The male and female patients were included at 1 to 1 ratio in the matched cohort. Finally, there were 4848 patients in the matched male group who were selected from 7555 original male patients and there were 4848 patients in the matched female group who were selected from 6860 original female patients (Fig. 1).

2.3. Study outcomes

The study endpoints included acute myocardial infarction (AMI), unstable angina, acute coronary syndrome (ACS) (AMI + unstable angina), hemorrhagic stroke, ischemic stroke, other strokes defined as undetermined types of stroke and stroke sequela, all strokes defined as ischemic, hemorrhagic, and other strokes, vascular procedures, and in-hospital mortality. The vascular procedures included carotid angioplasty and endarterectomy, coronary angioplasty/stenting and coronary artery bypass grafting surgery, and peripheral angioplasty and lower extremity amputation. In patients reaching the study endpoints, they were followed until the first episode of adverse cardiovascular events. The other patients were followed until December 2008. The full ICD-9-CM of CVD, CAD, PAD, related procedure codes, comorbidities, and outcomes are provided in the Supplementary Table, http://links.lww.com/MD/E110.

2.4. Statistical analysis

Categorical variables among groups were compared by Chi-square analysis. Continuous variables among groups were compared by one-way analysis of variance. Time to cardiovascular events was assessed by Cox regression analysis. In the multivariate analysis, we adjusted monthly income, urbanization level, hospital level, and many important comorbidities and medication, including age, DM, hypertension, hyperlipidemia, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, aortic and mitral valve stenosis, peptic ulcer disease, using of anti-thrombotic agents, using of anti-hypertensive agents, using of anti-diabetic agents, using of lipid-lowing agents, and using of proton pump inhibitors. Significance was set at $P < .05$. All the data processing and statistical analyses were performed with SAS 9.3 software.

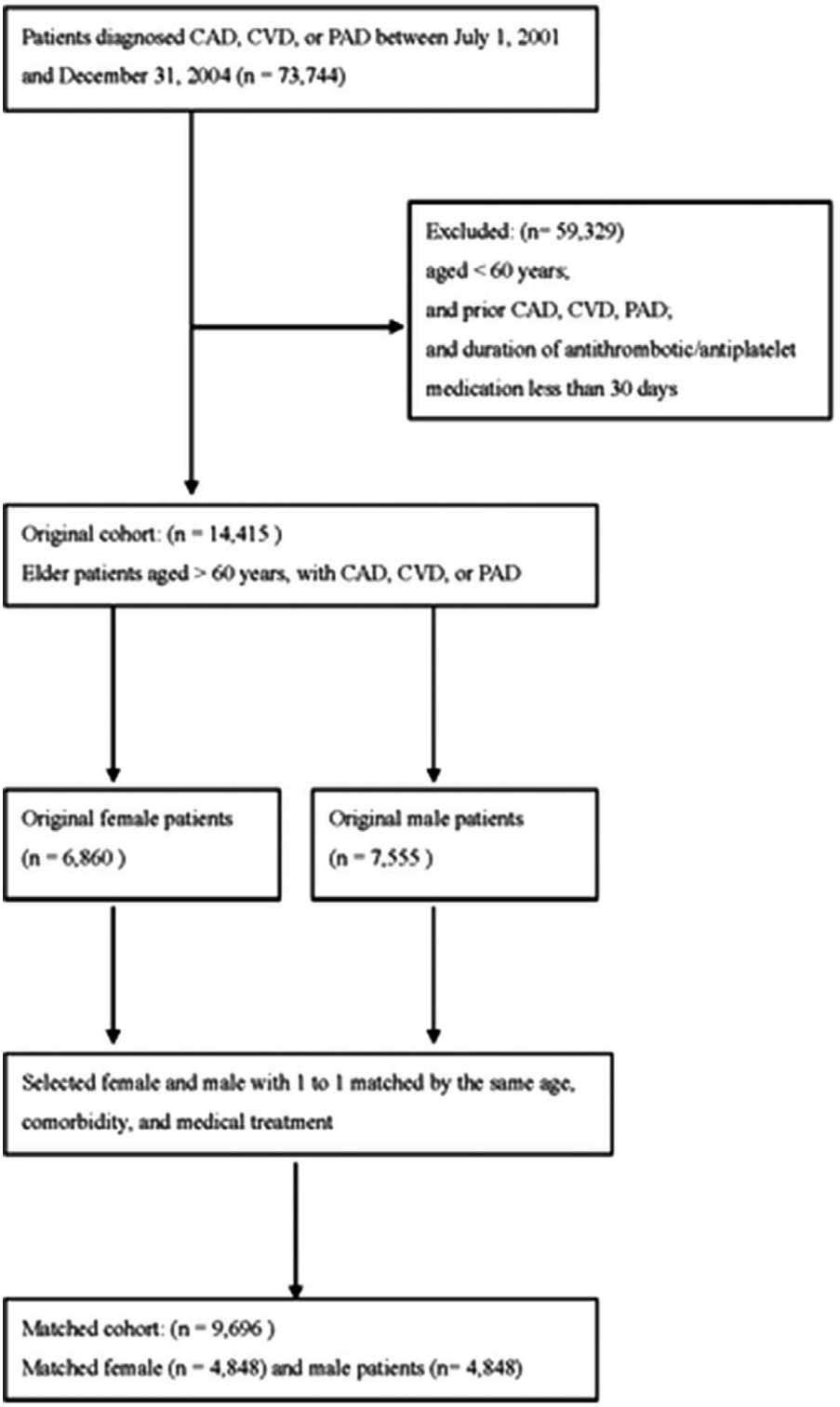

Figure 1. Flow chart of our old study patients with atherosclerotic cardiovascular diseases. CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

3. Result

Of the 14,415 patients aged over 60 years diagnosed as CVD, CAD, or PAD from January 2001 to December 2004, finally, 9696 patients (50% male) met all the inclusion criteria (Fig. 1). The mean age was 70.53 ± 6.58 years-old. Table 1 shows the comparison of baseline characteristics between male and female patients in original and matched cohorts. There were differences in DM, hypertension, hyperlipidemia, congestive heart failure, chronic kidney diseases, chronic obstructive pulmonary disease,

Table 1

Baseline characteristics of the original and matched cohorts in old patients with atherosclerotic cardiovascular diseases.

Variables/groups, N (%)	Original cohort (n = 14,415)			Matched cohort (n = 9,696)		
	Female n = 6,860 (47.6)	Male n = 7,555 (52.4)	*P*	Female n = 4,848 (50.0)	Male n = 4,848 (50.0)	*P*
Age (mean ± SD)	71.16 ± 6.83	71.07 ± 7.09	.4420	70.56 ± 6.58	70.50 ± 6.58	1.0000
Diabetes mellitus	2194 (32.0)	1926 (25.5)	<.0001	1338 (27.6)	1338 (27.6)	1.0000
Hypertension	4731 (69.0)	4741 (62.8)	<.0001	3378 (69.7)	3378 (69.7)	1.0000
Hyperlipidema	1637 (23.9)	1319 (17.5)	<.0001	855 (17.6)	855 (17.6)	1.0000
Congestive heart failure	602 (8.8)	550 (7.3)	.0009	111 (2.3)	111 (2.3)	1.0000
Atrial fibrillation	176 (2.6)	210 (2.8)	.4267	12 (0.2)	12 (0.2)	1.0000
Chronic kidney disease	182 (2.7)	275 (3.6)	.0007	23 (0.5)	23 (0.5)	1.0000
Chronic obstructive pulmonary disease	911 (13.3)	1608 (21.3)	<.0001	402 (8.3)	402 (8.3)	1.0000
Aortic and mitral valve stenosis	121 (1.8)	113 (1.5)	.2033	4 (0.1)	4 (0.1)	1.0000
Peptic ulcer disease	1518 (22.1)	1657 (21.9)	.7770	769 (15.9)	769 (15.9)	
Medication						1.0000
Anti-thrombotic agents	6838 (99.7)	7523 (99.6)	.3127	4848 (100.0)	4848 (100.0)	1.0000
Anti-hypertensive agents	6599 (96.2)	7170 (94.9)	.0002	4747 (97.9)	4747 (97.9)	1.0000
Anti-diabetic agents	2720 (39.7)	2368 (31.3)	<.0001	1755 (36.2)	1755 (36.2)	1.0000
Lipid-lowering agents	3370 (49.1)	3078 (40.7)	<.0001	2310 (47.6)	2310 (47.6)	1.0000
Proton pump inhibitors	2342 (34.1)	2687 (35.6)	.0728	1532 (31.6)	1532 (31.6)	
Monthly income			<.0001			<.0001
0	3199 (46.5)	2325 (30.8)		2291 (47.3)	1581 (32.6)	.
NT$ 1–20,000	3364 (49.0)	4753 (62.9)		2358 (48.6)	2930 (60.4)	.
NT$ >20,000	297 (4.3)	477 (6.3)		199 (4.1)	337 (7.0)	
Urbanization level			.3308			.0106
1	1464 (21.3)	1645 (21.8)		1035 (21.3)	1140 (23.5)	.
2	463 (6.7)	534 (7.1)		329 (6.8)	300 (6.2)	.
3	255 (3.7)	310 (4.1)		175 (3.6)	219 (4.5)	.
4	3039 (44.3)	3368 (44.6)		2154 (44.4)	2115 (43.6)	.
5	1619 (23.6)	1681 (22.3)	.	1139 (23.5)	1062 (21.9)	
Hospital level			<.0001			<.0001
Medical center	391 (5.7)	453 (6.0)		269 (5.5)	282 (5.8)	
Regional hospital	316 (4.6)	548 (7.3)		228 (4.7)	339 (7.0)	
District hospital	1271 (18.5)	1553 (20.6)		889 (18.3)	933 (19.2)	
Clinics	4882 (71.2)	5001 (66.2)		3462 (71.4)	3294 (67.9)	

received multiple medications, and social economic levels between male and female patients with ASCVD in the original cohort. After matching female with male by age, baseline comorbidities, and medical treatments, there were still significant differences in monthly income, urbanization level, and hospital level between female and male patients in matched cohort (Table 1).

Table 2 shows the hazard ratios (HRs) of adverse cardiovascular events in the matched cohort. The event rates of ACS, all strokes, vascular procedure, in-hospital mortality, and ischemic stroke were higher in male patients than female patients in matched cohort ($P \leqq .0017$). After adjustment for age, baseline comorbidities, medical treatments, monthly income, urbanization level, and hospital level, the adjusted HRs of female patients in predicting ACS, all strokes, vascular

Table 2

Adverse cardiovascular events between female and male groups in original and matched cohorts.

Variables/groups, N (%)	Original cohort, n = 14,415				Matched cohort, n = 9,696			
	Total original patients	Female n = 6,860	Male n = 7,555	*P*	Total matched patients	Female n = 4,848	Male n = 4,848	*P*
Acute coronary syndrome	1408 (9.8)	601 (8.8)	807 (10.7)	.0001	910 (9.4)	381 (7.9)	529 (10.9)	<.0001
Acute myocardial infarction	858 (6.0)	349 (5.1)	509 (6.7)	<.0001	564 (5.8)	226 (4.7)	338 (7.0)	<.0001
Unstable angina	904 (6.3)	408 (5.9)	496 (6.6)	.1266	546 (5.6)	257 (5.3)	289 (6.0)	.1586
All strokes	4276 (29.7)	1904 (27.8)	2372 (31.4)	<.0001	2921 (30.1)	1325 (27.3)	1596 (32.9)	<.0001
Hemorrhagic stroke	653 (4.5)	253 (3.7)	400 (5.3)	<.0001	419 (4.3)	178 (3.7)	241 (5.0)	.0017
Ischemic stroke	2916 (20.2)	1289 (18.8)	1627 (21.5)	<.0001	2016 (20.8)	898 (18.5)	1118 (23.1)	<.0001
Other strokes	2631 (18.3)	1148 (16.7)	1483 (19.6)	<.0001	1800 (18.6)	791 (16.3)	1009 (20.8)	<.0001
Vascular procedures	2226 (15.4)	830 (12.1)	1396 (18.5)	<.0001	1495 (15.4)	568 (11.7)	927 (19.1)	<.0001
In hospital mortality	1102 (7.6)	433 (6.3)	669 (8.9)	<.0001	651 (6.7)	278 (5.7)	373 (7.7)	.0001

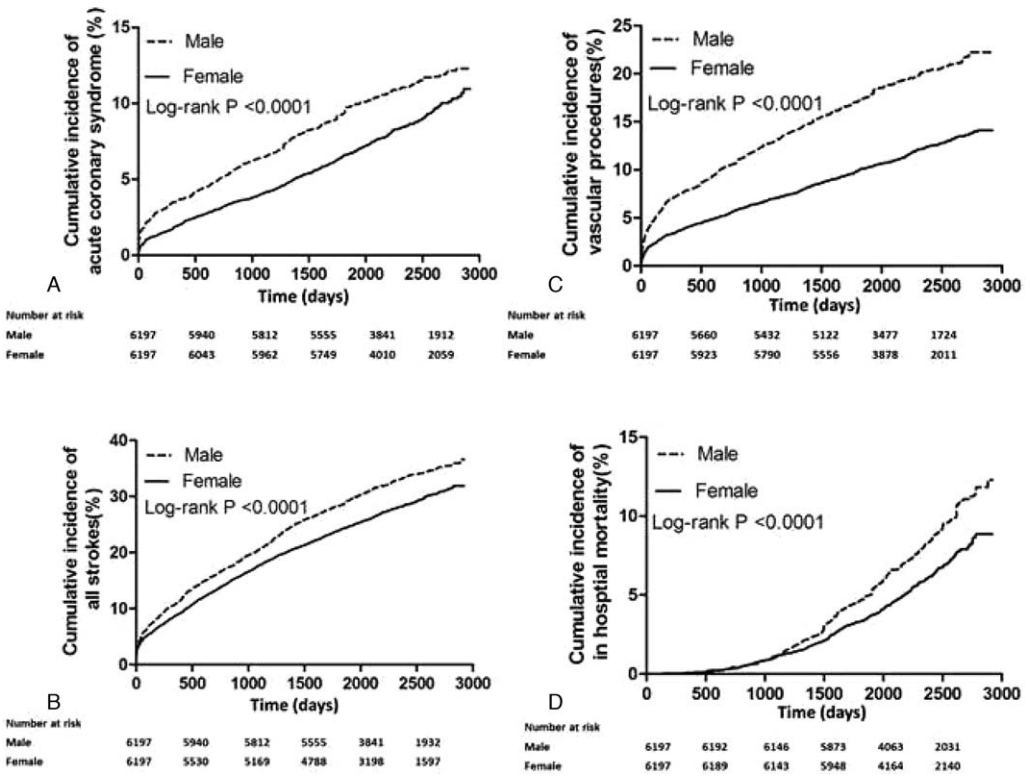

Figure 2. Kaplan–Meier cumulative risk curves for adverse cardiovascular events (A, acute coronary syndrome; B, all strokes; C, vascular procedures; D, in hospital mortality) in old male and female patients with atherosclerotic cardiovascular diseases.

procedures, and in hospital mortality in matched cohort were 0.71, 0.80, 0.59, and 0.77, respectively ($P \leqq .0007$). Figure 2 demonstrates the Kaplan–Meier cumulative risk curves for the ACS, all strokes, vascular procedures, and in hospital mortality in old patients with atherothrombotic diseases. There were significant differences in these four cardiovascular outcomes between old female and male patients (all Log-rank $P < .0001$) (Fig. 2A–D) (Table 3).

4. Discussion

In the retrospective population-based cohort study, we demonstrated that the impact of gender on subsequent adverse cardiovascular outcomes among age over 60 year-old patients with atherothrombotic diseases. In the matched cohort, the subsequent adverse cardiovascular events including ACS, all strokes, vascular procedures, and in hospital mortality were significantly lower in female patients than in male patients both in univariate and multivariate analyses.

Table 3

The adjusted hazard ratios for female group in predicting adverse cardiovascular events in matched cohort.

Variables	Adjusted hazard ratio (95% CI)	*P*
Acute coronary syndrome	0.71 (0.62–0.81)	<.0001
Acute myocardial infarction	0.67 (0.56–0.79)	<.0001
Unstable angina	0.89 (0.75–1.05)	.1686
All strokes	0.80 (0.74–0.86)	<.0001
Hemorrhagic stroke	0.73 (0.60–0.79)	.0015
Ischemic stroke	0.78 (0.71–0.85)	<.0001
Other strokes	0.77 (0.70–0.85)	<.0001
Vascular procedures	0.59 (0.53–0.65)	<.0001
In hospital mortality	0.77 (0.65–0.89)	.0007

Traditional atherosclerotic risk factors are age, hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking.[25] From previous studies, risk factors for CAD in hospital-based geriatric patients are smoking (odds ratio = 6.667 for men), hypertension (odds ratio = 3.276 for men, odds ratio = 2.695 for women), high-density lipoprotein (odds ratio = 0.832 for men, odds ratio = 0.830 for women), and low-density lipoprotein (odds ratio = 1.098 for men, odds ratio = 1.090 for women).[26] Optimal medical therapies for old Taiwanese with hypertension and diabetes were also important health-care issues.[27,28] Similar to previous studies, diabetes, hypertension, and dyslipidemia were significantly higher in female group in our original cohort. Although, traditional ASCVD risk factors were not different between male and female groups in the present match cohort, we should manage risk factors according to current guideline recommendations.

Except traditional atherosclerotic risk factors, menopause and hormone replacement therapy were another atherosclerotic risk factors in old female patients.[29] The incidence of ASCVD and adverse cardiovascular events has increased in women with menopause.[30] There were multi-factorial etiologies of poor cardiovascular outcomes in menopausal women. In post-menopausal women, there were unfavorable lipid profiles, including increased serum total cholesterol and low-density cholesterol and decreased serum high-density cholesterol.[31,32] Hormone replacement therapies were important issue in menopausal women. The possible mechanisms of thrombosis

induced by hormone replacement therapies were increased pro-thrombotic phenomenon, such as increased levels of coagulation activators, increased pro-thrombin fragments, reduced levels of anti-coagulants, and reduced free tissue factor pathway inhibitors.[33] Although female CAD patients frequently presented with atypical chest pain and were older than man CAD patients, pharmacological therapies for CAD were similar between them.[34] Female ACS patients have lower percentage of receiving lipid-lowering agents and more unfavorable lipid profiles than male ACS patients in the Tromsø Study.[34,35] In patients treated with primary percutaneous coronary intervention, female patients had higher mortality than male patients even after adjusting baseline comorbidities and medications in a meta-analysis study.[36] Previous study demonstrated there was a significant association between age and the mortality risk of percutaneous coronary intervention relative to coronary artery bypass grafting surgery, but there was no significant sex-related difference in the mortality risk of percutaneous coronary intervention relative to coronary artery bypass grafting surgery.[36] In addition, another previous study showed younger age was associated with higher 30-day mortality rates in women with ST segment elevation myocardial infarction even after adjustment for medications, primary percutaneous coronary intervention, and other coexisting comorbidities, but this difference declined after age 60 and was no longer observed in oldest women (≥75 year-old).[36]

Young female patients with ACS experienced higher mortality rate than male even after adjusted confounding factors in observation studies.[37–39] Mortality difference was not observed in the older female ACS patients over 70 years of age in Asian population.[39] In the aspect of stroke, older female patients had higher mortality than male patients in Taiwan from 1989 to 1993.[28] However, mortality rate was not different in gender in Taiwanese with acute ischemic stroke from 2007 to 2014.[40] Unlike previous studies, elder female patients over 60 years of age with ASCVD had significantly lower rate of ACS, all strokes, vascular procedures, and in hospital mortality than male after adjusting multiple variables in our study cohort. First, the major difference between our study and previous studies was inclusion criteria. In our present study, we included first diagnosed ASCVD elder patients who had received medications at least 30 days. Those selected patients may be stable ASCVD in our study. Second, some possible confounders were difficult took into our study. Because of lack of suitable indication of oral contraceptive and hormone replace therapies in young age in National Health Insurance, these factors were not adjusted in our study. We also did not totally matched gender difference regarding in social economic state and residence area.

There were several limitations in our population-based longitudinal investigation. First, the life-style characteristics, body mass index, and laboratory data were lacking in the Health Insurance Research Dataset. Second, age of menopause was an important cardiovascular risk factor, which could influence the amount of accumulated visceral adipose tissue, but we had no such data.[41] Third, the characteristics of coronary angiography was lack in our study. Significant coronary artery disease with left main involved was a life-threatening condition. Patients with left main diseases managed revascularization strategies, such as coronary artery bypass graft and percutaneous coronary intervention should be considered their age, comorbidity, stay of hospitalization, and safety-profiles.[42] Fourth, management of large thrombus burden in coronary artery, such as rheolytic thrombectomy and manual thrombus aspiration were important in AMI patients with high risk for distal coronary thrombotic embolization. These managements could be also provided better long term outcome in AMI patients.[43] However, strategies of revascularization and thrombus managements were also lack in the present study.

5. Conclusion

In this population-based propensity matched cohort study, age over 60 year-old female patients with ASCVD were associated with lower rates of ACS, AMI, strokes, vascular procedures, and in-hospital mortality than male patients. Further prospective studies may be investigated in Taiwan.

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