

Sex difference in clinical outcomes of Chinese patients with atrial fibrillation and coronary stenting according to age

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ABSTRACT

Objective: Sex differences in the clinical outcomes of patients with atrial fibrillation (AF) and coronary stenting should be assessed according to age.

Methods: We analyzed the clinical data of all patients with nonvalvular AF who underwent coronary stenting between January 2010 and June 2015 in 12 hospitals of Beijing, China.

Results: A total of 2,146 patients (71.8% men and 28.2% women) were included in the study. The mean age of the patients was 66.6±9.4 years. Women in this study were older and had higher prevalence of hypertension, diabetes, chronic kidney disease (CKD), and anemia. Smoking history was found to be higher in men, and women were less likely to be current smokers. The mean follow-up duration was 39.7 months. Women younger than 65 years had a remarkably higher mortality (11.2% vs. 5.3%, $p=0.012$) and a significantly lower rate of repeat revascularization (1.6% vs. 6.3%, $p=0.034$) than men. Female gender remained an independent predictor for all-cause mortality [hazard ratio (HR)=2.03, 95% confidence interval (CI): 1.09–3.79, $p=0.025$], along with heart failure (HR=3.64, 95% CI: 2.02–6.57, $p<0.001$) and CKD (HR=2.46, 95% CI: 1.09–5.57, $p=0.031$) after multivariate regression analysis. No significant difference was noted between men and women with regard to mortality, ischemic events, and major bleeding in elderly patients.

Conclusion: In Chinese patients younger than 65 years with AF and coronary stenting, female gender was independently associated with increased mortality; men were more likely to receive repeat revascularization possibly due to the current smoking. Whether it was a biological difference or a recognition disparity of the disease between men and women warrants further investigation.

Keywords: sex, age, atrial fibrillation, percutaneous coronary intervention, mortality

Cite this article as: Zheng JY, Li DT, Chen Y, Tang YD, Guo CJ, Chen YD, et al. Sex difference in clinical outcomes of Chinese patients with atrial fibrillation and coronary stenting according to age. *Anatol J Cardiol* 2021; 25: 17-23

Introduction

Coronary artery disease (CAD) and atrial fibrillation (AF) are the most common heart diseases in hospitalized patients. These two conditions may coexist in the same patient as both have many common risk factors. Approximately, 4.5%–12.3% of patients undergoing percutaneous coronary intervention (PCI) had AF (1-5). In a Japanese cohort, about 1% of AF patients underwent PCI annually, with the incidence increasing with more risk factors (6). In recent years, patients with AF and coronary stent-

ing have intrigued cardiologists due to their worse prognosis and controversy over the optimal antithrombotic strategy (1-4).

CAD and AF affect men and women differently. Women had a 10-year delayed onset of CAD. Young women with premature CAD had a distinctive risk profile and pathophysiology from men (7, 8), and the sex differences narrowed with increasing age. Controversy remains whether sex differences still exist in the prognosis of patients undergoing PCI in the current era, even in large national registries (9-11). Ischemic stroke and systemic thromboembolism seemed to occur more frequently in women

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Accepted Date: 07.07.2020 **Available Online Date:** 07.12.2020

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DOI:10.14744/AnatolJCardiol.2020.80930



than men with AF, as evidenced by CHA₂DS₂-VASc score. Therefore, sex differences might exist in the clinical outcomes of patients with AF undergoing PCI, and should be vigilantly assessed according to age, due to profound interaction between age and sex. In this multicenter study, we aimed to illustrate the clinical features of a Chinese cohort with AF and coronary stenting according to age and sex and evaluate whether sex independently affected mortality and major adverse cardiovascular events of this population.

Methods

We enrolled patients with concomitant CAD and nonvalvular AF who underwent PCI with stenting between January 2010 and June 2015 in 12 hospitals of Beijing, China. The enrolled patients should have been previously diagnosed as AF in any specialized medical institution, or have AF recorded on electrocardiogram (ECG) or ambulatory monitoring before PCI. Patients who had AF initially detected after PCI were excluded. In this study, we did not include patients with ST-segment elevation myocardial infarction (MI), because (1) new-onset AF might occur in this situation and usually resolved before discharge; (2) the pathogenesis of the transient AF could be the result of atrial infarction in the situation of inferior MI, or related to circulatory collapse due to massive MI. Patients' clinical data, including risk factors, past history, blood tests, clinical diagnosis, AF type, PCI information, and use of medication, were collected. All patients were followed up either in the outpatient departments or by telephone. Each death was confirmed with the National Demographic Registry. We stratified eligible patients according to their ages (<65 and ≥65 years) and compared the clinical characteristics and outcomes between men and women.

Creatinine clearance for each patient was calculated with the Cockcroft–Gault equation. Chronic kidney disease (CKD) was defined as moderate-to-severe renal dysfunction with estimated creatinine clearance of <60 mL/min/. Heart failure denoted symptomatic heart failure and/or a reduced left ventricular ejection fraction <50%. We defined the major adverse cardiac/cerebrovascular events (MACCE) as a composite of all-cause death, nonfatal MI, repeat revascularization, ischemic stroke, and peripheral artery thromboembolism. Bleeding events were assessed with the use of Bleeding Academic Research Consortium (BARC) criteria, and grade 2 or higher was considered as a major bleeding event.

The study was conducted in accordance with the ethical guidelines in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the institution. All patients had given written informed consents to participate in the study.

Statistical analysis was performed using IBM SPSS Statistics version 20.0. Normality test was done to know the distribution of continuous variables. Normally distributed continuous variables were expressed as mean and standard deviation and

compared with independent samples t test; non-normally distributed continuous variables were presented as median (interquartile range) and compared with the Mann–Whitney U test. Categorical variables were presented as numbers (percentage) and compared with Pearson's chi-square or Fisher's exact test. Cox's proportional hazards regression model was adopted to correct the baseline imbalances between men and women. Hazard ratio (HR) with its 95% confidence interval (CI) was calculated to determine the effect of covariates on clinical outcomes. A two-sided p-value <0.05 was considered to be statistically significant.

Results

A total of 2,146 patients (1,540 men and 606 women) with a mean age of 66.6±9.4 years were included in the study. Table 1 showed the baseline clinical characteristics of the cohort according to age and sex. It was seen that women included in the study were older, had higher prevalence of hypertension, diabetes, CKD, and anemia, but were less likely to be current smokers compared to men. The sex differences were evident both in young and old populations, and more prominent in the elderly. Highest prevalence of hypertension and CKD was found among women >65 years with lowest mean estimated creatinine clearance among different age–sex groups.

Prevalence of non-ST-segment elevation MI, paroxysmal AF, heart failure, and multivessel stenting, irrespective of age, were found to be similar in men and women. All patients were treated with drug-eluting stents. Dual antiplatelet therapy was the dominant antithrombotic strategy in both sexes. There was significantly lesser use of statins among women >65 years than men.

The mean follow-up duration was 39.7±18.3 months. Complete follow-up data were obtained from 95.1% (women 94.6% vs. men 95.3%, p=0.497) of the study population. The total mortality during

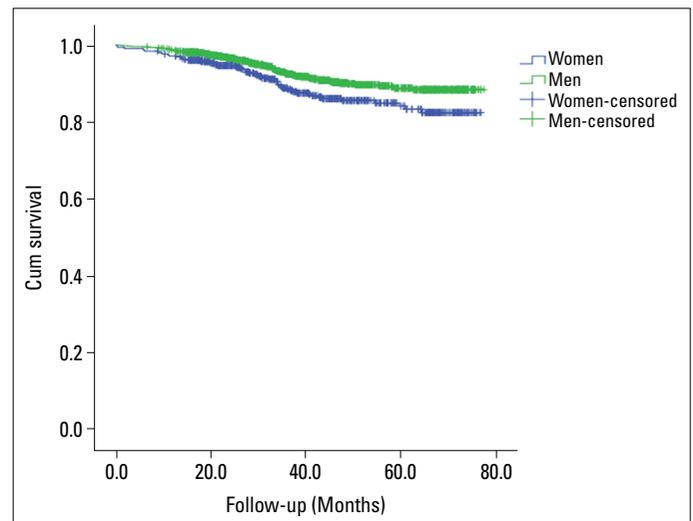


Figure 1. Kaplan–Meier survival analysis between men and women

Table 1. Baseline clinical characteristics according to age and sex

	Age <65 years			Age ≥65 years			Total		
	Men (n=719)	Women (n=127)	P-value	Men (n=821)	Women (n=479)	P-value	Men (n=1540)	Women (n=606)	P-value
Age (years)	58.0 (53.0, 62.0)	60.0 (57.0, 63.0)	<0.001	72.0 (68.0, 76.0)	73.0 (69.0, 77.0)	0.039	65.0 (59.0, 73.0)	71.0 (66.0, 76.0)	<0.001
Hypertension, n (%)	501 (69.7)	92 (72.4)	0.543	614 (74.8)	397 (82.9)	0.001	1115 (72.4)	489 (80.7)	<0.001
Diabetes, n (%)	221 (30.7)	48 (37.8)	0.115	247 (30.1)	167 (34.9)	0.074	468 (30.4)	215 (35.5)	0.023
Current smoker, n (%)	487 (67.7)	8 (6.3)	<0.001	402 (49.0)	51 (10.6)	<0.001	889 (57.7)	59 (9.7)	<0.001
Prior MI, n (%)	16 (2.2)	2 (1.6)	0.893	36 (4.4)	16 (3.3)	0.354	52 (3.4)	18 (3.0)	0.633
Prior PCI, n (%)	136 (18.9)	23 (18.1)	0.831	174 (21.2)	97 (20.3)	0.686	310 (20.1)	120 (19.8)	0.864
Prior CABG, n (%)	19 (2.6)	6 (4.7)	0.321	42 (5.1)*	12 (2.5)*	0.023	61 (4.0)	18 (3.0)	0.273
Prior ischemic stroke, n (%)	81 (11.3)	20 (15.7)	0.151	129 (15.7)	78 (16.3)	0.786	210 (13.6)	98 (16.2)	0.132
Prior intracranial hemorrhage, n (%)	2 (0.3)	0	1.000	5 (0.6)	2 (0.4)	0.950	7 (0.5)	2 (0.3)	0.975
Prior gastrointestinal bleeding, n (%)	2 (0.3)	0	1.000	3 (0.4)	2 (0.4)	1.000	5 (0.3)	2 (0.3)	1.000
Anemia, n (%)	26 (3.6)	36 (28.3)	<0.001	107 (13.0)	155 (32.4)	<0.001	133 (8.6)	191 (31.5)	<0.001
Hemoglobin (g/L)	146.6±14.9	128.2±14.8	<0.001	138.1±17.1	125.5±15.1	<0.001	142.1±16.6	126.1±15.1	<0.001
Hematocrit (%)	42.8±4.1	38.2±4.3	<0.001	40.8±4.7	37.7±4.3	<0.001	41.7±4.6	37.8±4.3	<0.001
Estimated creatinine clearance (mL/min)	97.9±25.9	84.3±24.7	<0.001	70.3±18.6	65.7±19.5	<0.001	83.2±26.2	69.6±22.0	<0.001
CKD, n (%)	24 (3.3)	12 (9.4)	<0.001	242 (29.5)	201 (42.0)	<0.001	266 (17.3)	213 (35.1)	<0.001
NSTEMI, n (%)	121 (16.8)	19 (15.0)	0.601	153 (18.6)	86 (18.0)	0.760	274 (17.8)	105 (17.3)	0.799
Paroxysmal AF, n (%)	563 (78.3)	103 (81.1)	0.477	636 (77.5)	389 (81.2)	0.111	1199 (77.9)	492 (81.2)	0.089
Heart failure, n (%)	94 (13.1)	18 (14.2)	0.736	117 (14.3)	78 (16.3)	0.322	211 (13.7)	96 (15.8)	0.202
Multivessel stenting, n (%)	161 (22.4)	23 (18.1)	0.281	198 (24.1)	113 (23.6)	0.830	359 (23.3)	136 (22.4)	0.667
Number of stents	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.247	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.830	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.633
Antithrombotic strategy									
Triple therapy, n (%)	43 (6.0)	6 (4.7)	0.576	42 (5.1)	17 (3.5)	0.191	85 (5.5)	23 (3.8)	0.100
Dual antiplatelets, n (%)	670 (93.2)	119 (93.7)	0.831	771 (93.9)	452 (94.4)	0.738	1441 (93.6)	571 (94.2)	0.574
One antiplatelet plus one oral anticoagulant, n (%)	6 (0.8)	2 (1.6)	0.766	8 (1.0)	10 (2.1)	0.098	14 (0.9)	12 (2.0)	0.041
β-receptor blockers, n (%)	563 (78.3)	106 (83.5)	0.187	611 (74.4)	361 (75.4)	0.705	1174 (76.2)	467 (77.1)	0.684
ACEI/ARB, n (%)	435 (60.5)	77 (60.6)	0.978	488 (59.4)	300 (62.6)	0.256	923 (59.9)	377 (62.2)	0.331
Statins, n (%)	686 (95.4)	123 (96.9)	0.464	787 (95.9)	439 (91.6)	0.002	1473 (95.6)	562 (92.7)	0.006
PPI, n (%)	151 (21.0)	21 (16.5)	0.249	209 (25.5)	126 (26.3)	0.736	360 (23.4)	147 (24.3)	0.665

Heart failure refers to symptomatic heart failure and/or a reduced left ventricular ejection fraction less than 50%. Creatinine clearance is calculated based on Cockcroft-Gault formula. CKD refers to moderate-to-severe renal dysfunction with estimated creatinine clearance <60 mL/min.
 ACEI - angiotensin-converting enzyme inhibitor; AF - atrial fibrillation; ARB - angiotensin receptor blocker; CABG - coronary artery bypass grafting surgery; CKD - chronic kidney disease; MI - myocardial infarction; PCI - percutaneous coronary intervention; PPI - proton pump inhibitor; NSTEMI - non-ST-segment elevation myocardial infarction

Table 2. Clinical outcomes after PCI according to age and sex

	Age <65 years			Age ≥65 years			Total		
	Men (n=695)	Women (n=125)	P-value	Men (n=772)	Women (n=448)	P-value	Men (n=1467)	Women (n=573)	P-value
Death, n (%)	37 (5.3)	14 (11.2)	0.012	68 (8.8)	50 (11.2)	0.180	105 (7.2)	64 (11.2)	0.003
Myocardial infarction, n (%)	2 (0.3)	2 (1.6)	0.112	6 (0.8)	9 (2.0)	0.60	8 (0.5)	11 (1.9)	0.004
Target vessel revascularization, n (%)	44 (6.3)	2 (1.6)	0.034	32 (4.1)	13 (2.9)	0.267	76 (5.2)	15 (2.6)	0.012
Ischemic stroke, n (%)	14 (2.0)	2 (1.6)	1.000	36 (4.7)	21 (4.7)	0.985	50 (3.4)	23 (4.0)	0.508
Systemic thromboembolism, n (%)	14 (2.0)	2 (1.6)	1.000	37 (4.8)	24 (5.4)	0.663	51 (3.5)	26 (4.5)	0.258
MACCE, n (%)	94 (13.5)	18 (14.4)	0.793	132 (17.1)	85 (19.0)	0.409	226 (15.4)	103 (18.0)	0.156
Major bleeding, n (%)	22 (3.2)	3 (2.4)	0.861	24 (3.1)	11 (2.5)	0.510	46 (3.1)	14 (2.4)	0.406
BARC grade 2, n (%)	14 (2.0)	2 (1.6)	1.000	14 (1.8)	8 (1.8)	0.972	28 (1.9)	10 (1.7)	0.806
BARC grade ≥3, n (%)	8 (1.2)	1 (0.8)	1.000	10 (1.3)	3 (0.7)	0.461	18 (1.2)	4 (0.7)	0.299

BARC - Bleeding Academic Research Consortium criteria; MACCE - major adverse cardiac/cerebrovascular events; PCI - percutaneous coronary intervention

follow-up was 8.3% with two in-hospital deaths (0.10%). Table 2 compared the clinical outcomes between men and women after PCI. Overall, women had a significantly higher incidence of all-cause death (Fig. 1) and MI but were less likely to receive repeat revascularization. There was no significant sex difference in ischemic stroke, systemic thromboembolism, MACCE, and major bleeding. Women younger than 65 years had a remarkably higher mortality and a significantly lower rate of repeat revascularization than men. No significant difference was observed between men and women with respect to death, ischemic events, and major bleeding complications in older population.

Univariate analysis on mortality suggested that HR for women younger than 65 years was 2.15 (95% CI: 1.16–3.98). After multivariate regression analysis with adjustment of baseline imbalance, female remained to be an independent predictor for all-cause death (HR=2.03, 95% CI: 1.09–3.79, $p=0.025$), along with heart failure (HR=3.64, 95% CI: 2.02–6.57, $p<0.001$) and CKD (HR=2.46, 95% CI: 1.09–5.57, $p=0.031$). The only independent risk factors for mortality were heart failure (HR=2.05, 95% CI: 1.37–3.08, $p=0.001$) and CKD (HR=2.32, 95% CI: 1.61–3.35, $p<0.001$) for older patients.

Discussion

This multicenter observational study demonstrated that Chinese women with AF and coronary stenting had a different clinical profile than men, and this sex difference was evident in both younger and older patients. However, no significant sex differences were found with respect to ischemic stroke, MACCE, and major bleeding during the follow-up period. The sex difference in mortality was related to age. Female gender was independently associated with increased mortality only in those younger than 65 years.

Our Chinese cohort with AF and coronary stenting were older (66.6±9.4 years vs. 61.7±11.4 years) and had an increased

prevalence of hypertension (74.7% vs. 60.2%), diabetes (31.8% vs. 21.8%), and CKD (22.3% vs. 13.1%) compared to the study population of a multicenter PCI registry in China (12). This finding was in agreement with literatures from western countries, in which relative to those without a history of AF, AF patients undergoing PCI often had an advanced age and were more likely to have comorbidities such as hypertension, diabetes, congestive heart failure, or renal insufficiency (2-4). The difference reflected the phenomenon that AF usually occurred with aging and accumulating risk factors.

The vast majority of our study population had paroxysmal AF who did not receive oral anticoagulants. There seemed to be a relatively lower AF burden with less detrimental effects in our cohort. However, the indication for anticoagulation was dictated by CHADS₂ or CHA₂DS₂-VASc score. Our cohort had a relatively lower CHADS₂ (1.7±1.2 vs. 2.5±1.3), CHA₂DS₂-VASc (3.6±1.5 vs. 4.0±1.6), and incidence of ischemic stroke (3.6% vs. 4.7%) than a Japanese cohort, in which 69.4% were men and 54.8% received oral anticoagulants (1). These differences could result from much younger ages (66.6±9.4 years vs. 75.7±7.6 years) in our study, because a comparable incidence of ischemic stroke (4.7%) was observed among patients older than 65 years. Although clinical outcomes of most studies favored oral anticoagulants in AF patients undergoing PCI, anticoagulants were inadequately used in real-world clinical practice. In a German study, only 26.8% of patients with CHADS₂ score of 2 or more received vitamin-K antagonists in any combination (4). However, no significant difference was noted in ischemic stroke or transient ischemic attack whether or not patients received warfarin (1.4% vs. 1.7%) (4).

Dual antiplatelet therapy was used predominantly in our Chinese cohort irrespective of estimated thrombotic and bleeding risks. This finding reflected the current situation on anti-thrombotic therapy in patients with AF and coronary stenting in China, and contrasted with previous observational studies from other countries, in which warfarin or novel oral anticoagulants

(NOAC)-based therapy was the preferred antithrombotic strategy in AF patients undergoing PCI (13, 14). As NOAC were not covered by the Beijing medical insurance system, therefore were not widely used in China during the study period. Before the advent of NOAC, warfarin was used as an effective agent to reduce cerebral thromboembolic risk in this population (15-17). However, it was inadequately used in the general population with AF in China. In a multicenter registry from 50 hospitals in China, 86.2% of patients with nonvalvular AF had CHADS₂ score ≥ 1 , but only 42.6% were on warfarin (18). The most common reasons for the inadequate anticoagulation were patient's unwillingness to receive regular international normalized ratio monitoring (43.0%) and concern of high risk of bleeding (33.3%) (18). Another possible reason in this study population might be the concern of many Chinese cardiologists about the risk of excessive bleeding after coronary stenting when warfarin was combined with antiplatelet agents.

As with other studies searching patients with or without AF undergoing PCI, women were on average 5 years older and had more comorbidities than men in our study (9, 19, 20). Most of the previous studies indicated that women undergoing PCI had comparable prognosis with their male counterparts after adjustment of baseline imbalance (19, 21-23). However, a recent analysis on United States' national PCI cohort of 6.6 million patients demonstrated that women had a higher in-hospital mortality not fully accounted for by baseline comorbidities (9). Another analysis on the British-Swedish national PCI registry also suggested that female gender was an independent predictor of all-cause mortality at 30 days and 1 year (11). Propensity matching or multivariate regression analysis showed that women were more commonly suffered from ischemic events than men following PCI, including cardiac death, MI, stroke, and repeat revascularization (24, 25).

In view of potential interaction between age and sex, we believed sex difference should be evaluated according to age. In our study, women with AF and coronary stenting had shown a higher incidence of all-cause mortality and MI than men. Female gender was independently associated with mortality only in the younger population, however, the difference diminished after adjustment of baseline imbalance in the elderly. This finding was in agreement with a previous study conducted on patients of premature CAD (≤ 40 years), which suggested female gender was the only independent predictor of 1-year mortality or nonfatal MI following PCI (8). The National Heart, Lung, and Blood Institute Dynamic Registry also demonstrated that women younger than 50 years were at an increased risk of ischemia and revascularization compared with men at 5-year follow-up with PCI, however, clinical outcomes were found similar between older women and men (26).

In contrast to other studies, young women were less likely to undergo repeat revascularization than men in our study. The reason for the increased mortality and lower revascularization rate in younger women was unknown. This finding might be reason

why younger Chinese women were usually reluctant to undergo repeated invasive procedures and prolonged antithrombotic therapy in clinical practice despite having more comorbidities and higher risk of death. Men were found to be smoking at the time of PCI, and often unwilling or failed to quit smoking after the procedure. Smoking increased the risk of atherosclerotic burden and repeat revascularization. Thus, we considered that the sex difference per se might not be a biological or physiological difference but a recognition disparity of the disease between men and women. If this was the case, education on the potential risk during every consultation with cardiologists would help to eliminate the difference and improve the prognosis in both men and women. Further research is needed to carry out a systematic investigation on this issue.

A recent retrospective analysis suggested that only a minority of deaths were cardiac (33.8% in women, 38.0% in men) in the contemporary era of PCI (19). In our study, only 72 of the 169 deaths had a clear cause recorded. The most common cause of death was cardiac (55.6%) with 12 cases (16.7%) from acute MI. Other causes of death were reported to be sepsis with circulatory collapse (11.1%), ischemic stroke (5.6%), major bleeding (6.9%), hemorrhagic stroke (5.6%), renal failure (2.8%), malignancy (2.8%), accident (2.8%), and others (8.3%).

Few studies have investigated the potential risk factors in patients with AF undergoing PCI. Traditional risk scoring systems showed limited predictive ability for adverse cardiovascular events (27). In this study, we identified heart failure and CKD as independent predictors of death in both younger and older patients. Renal dysfunction was independently associated with 1-year all-cause mortality and MACCE in patients with AF referred for PCI in the AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry (28). One possible explanation is that CKD is often associated with other traditional cardiovascular risk factors. However, CKD per se disorders many aspects of the thrombotic process and complicates the metabolism of many cardiovascular drugs (29). Renal dysfunction promotes inflammation and activates neurohormonal signaling pathways, including sympathetic nervous and renin-angiotensin-aldosterone system. These pathophysiologic changes induce ischemia, myocardial dysfunction, and end-organ injury.

Study limitations

There are some limitations to this study. This study was not prospectively designed to assess the long-term prognosis of patients with AF and coronary stenting, and the data utilized for analysis were derived from 12 hospitals in Beijing. As with all studies involving multicenter databases and registries, there was no audit of data quality and precision. As an inherent nature of retrospective studies, some demographic and clinical information might be missing. We looked up the National Demographic Registry for the possible cause of death. The cause of death was missing, unclear, or inaccurate for a considerable number of patients in the registry. Thus, we could not discrimi-

nate cardiac from noncardiac death. All patients were treated with drug-eluting stents. As the stents came from many different manufactures and were coated with different drugs, these might influence clinical outcomes. The choice of stents and antithrombotic regimens was totally at the treating physician's discretion. However, this "real-world" nature is the strength of our study.

Conclusion

Chinese women with AF and who underwent coronary stenting were older and had higher prevalence of hypertension, diabetes, CKD, and anemia compared to men. No significant sex differences were noted with respect to death, ischemic, and bleeding events in the elderly patients (≥ 65 years). Women younger than 65 years had a higher adjusted mortality but a lower revascularization rate compared to men following PCI. Whether it was a biological difference or a recognition disparity of the disease between men and women needs further investigation.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – T.C.L.; Design – J.Y.Z., D.T.L., Y.C., T.C.L.; Supervision – Y.D.C.; Fundings – T.C.L.; Materials – Y.C., Y.D.T., C.J.G., Y.D.C., Z.M.M.; Data collection and/or processing – Y.C., Y.D.T., C.J.G., Z.M.M.; Analysis and/or interpretation – J.Y.Z., D.T.L., Y.C.; Literature search – J.Y.Z., D.T.L., Y.C.; Writing – J.Y.Z., D.T.L.; Critical review – J.Y.Z., Y.C., Y.D.T., C.J.G., Z.M.M., T.C.L.

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