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Original Article

Long-term Mortality, Thrombotic Risk and Bleeding Complications of Very Old Chinese Patients with Atrial Fibrillation and Coronary Stenting

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SUMMARY

Background: The long-term mortality, thrombotic risk and bleeding complications of very old patients (≥ 80 years) with atrial fibrillation (AF) and coronary stenting were less studied.
Methods: We enrolled 1504 patients ≥ 65 years with nonvalvular AF undergoing coronary stenting between January 2010 and June 2015 from 12 hospitals in Beijing, China.
Results: 164 patients (10.9%) had ages ≥ 80 years. Very old patients had higher prevalence of cardiac dysfunction, renal dysfunction (RD, creatinine clearance < 60 ml/min), anemia and acute ST segment elevation myocardial infarction (STEMI) than younger patients. The mean follow-up duration was 39.0 ± 18.7 months. Complete follow-up data was obtained for 94.3% of the whole cohort. Very old patients had higher mortality (22.8% vs. 10.6%, $p < 0.001$), more major adverse cardiac/cerebrovascular events (MACCE, 33.6% vs. 18.5%, $p < 0.001$), and major bleeding events (MB) (5.4% vs. 2.8%, $p = 0.150$) than younger controls. For very old patients, multivariate Cox regression identified cardiac dysfunction (HR: 2.564, 95% CI: 1.279–5.139, $p = 0.008$), RD (HR: 4.001, 95% CI: 1.518–10.546, $p = 0.005$) and STEMI (HR: 2.529, 95% CI: 1.275-5.013, $p = 0.008$) as independent predictors for all-cause death; cardiac dysfunction (HR: 2.590, 95% CI: 1.470–4.565, $p = 0.001$) and RD (HR: 4.204, 95% CI: 1.865–9.476, $p = 0.001$) as independent predictors for MACCE; cardiac dysfunction (HR: 2.417, 95% CI: 1.399–4.176, $p = 0.002$), RD (HR: 4.278, 95% CI: 1.997–9.164, $p < 0.001$) and STEMI (HR: 1.767, 95% CI: 1.008–3.097, $p = 0.047$) as independent predictors for the composite endpoint of MACCE and MB.
Conclusion: Very old patients with AF and coronary stenting had a poor long-term prognosis, with cardiac dysfunction and RD as independent risk factors.

1. Introduction

Symptomatic coronary artery disease is present in approximately 20% to 30% of both men and women older than 80 years of age. Percutaneous coronary intervention (PCI) has become the preferred revascularization modality for octogenarians in China, because of the conservative belief in Chinese people and high risk associated with coronary artery bypass surgery in very old patients. Approximately 4.5%–12.3% of patients undergoing PCI had atrial fibrillation (AF) and bear both coronary and cerebrovascular thrombotic risk.[1–5] Interventional treatment of octogenarians with concomitant coronary artery disease and AF should balance the thrombotic and bleeding risks. However, clinical trials on prognosis of patients with AF and coronary stenting always excluded those older than 80 years.[6] In this observational study, we aimed to illustrate the long-term mortality, thrombotic risk and bleeding complications of very old Chinese patients (≥ 80 years) with a history of AF undergoing coronary stenting, and investigate potential risk factors related to adverse cardiovascular events.

2. Material and methods

We enrolled consecutive elderly patients (≥ 65 years) who had a history of AF (irrespective of paroxysmal, persistent or permanent) or AF at presentation, and underwent PCI with stenting between January 2010 and June 2015 in the departments of cardiology of 12 hospitals in Beijing, China. We clearly included patients who presented with acute ST segment elevation myocardial infarction (STEMI) and whose AF reverted to sinus rhythm before discharge. Patients with AF related with valvular heart disease, congenital heart disease or other structural heart diseases were excluded. We divided the study cohort into patients ≥ 80 years (study group) and those between 65 and 79 years (control group).

Jian-Yong Zheng, Yu-Bin Wang and Bo-Yang Zhang contributed equally to this study, and should be considered as co-first authors.

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All eligible patients were followed up in the outpatient departments or by telephone. Each death was confirmed with the National Demographic Registry. We defined the major adverse cardiac/cerebrovascular events (MACCE) as a composite of all-cause death, non-fatal myocardial infarction, target vessel revascularization, ischemic stroke and other peripheral artery thromboembolisms. We graded bleeding events according to Bleeding Academic Research Consortium criteria, and regarded grade 2 or higher as a major bleeding event. We also noted occurrence of either MACCE or any major bleeding complication as a composite endpoint. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committee of our center. Informed consent was obtained from each patient at admission.

The statistical analysis was performed with SPSS version 20.0 (IBM Corp, Armonk [NY], United States). We compared the baseline characteristics and clinical outcomes between the two age groups using 2-independent-sample *t* test, $\chi 2$ or Fisher exact test. We used univariate and multivariate Cox proportional hazard regression to obtain independent risk factors for all-cause death, MACCE and composite endpoint in patients older than 80 years. Hazard ratio (HR) was calculated as a measure of strength for the impact of potential risk factors on clinical outcomes. A two-sided *p* value less than 0.05 was considered to be statistically significant.

3. Results

A total of 1504 patients were included in the study, with 164 patients (10.9%) ≥ 80 years. Table 1 showed the clinical characteristics at baseline according to presenting ages. Compared to those with relatively younger ages, very old patients had higher prevalence of cardiac dysfunction (symptomatic heart failure or a reduced left ventricular ejection fraction of less than 50%), renal dysfunction (RD, creatinine clearance < 60 ml/min), anemia and STEMI at presentation, but were less likely to be current smokers. None of the very old patients had a history of hemorrhagic stroke.

All patients were treated with drug eluting stents. Very old patients had higher CHA_2DS_2-VASc scores (4.6 ± 1.4 vs. 3.8 ± 1.5, $p < 0.001$) than younger patients, without significant difference in HAS-BLED scores (3.2 ± 0.7 vs. 3.1 ± 0.8, $p < 0.001$). Antithrombotic strategies did not differ significantly between the two groups, and dual antiplatelet therapy (DAPT) was the dominant strategy in both populations. Warfarin was commonly used as the adjunctive anticoagulant in the triple therapy, and newer oral anticoagulants (NOAC) were used only in three cases. Angiotensin converting enzyme inhibitors/angiotensin receptor blockers were less and proton-pump inhibitors were more commonly used in very old patients.

The mean follow-up duration was 39.0 ± 18.7 months. Complete follow-up data was obtained for 94.3% (90.9% in the study group and 94.8% in the control group) of the whole cohort. Very old patients had almost doubled incidences of death (22.8% vs. 10.6%, $p < 0.001$), MACCE (33.6% vs. 18.5%, $p < 0.001$), major bleeding events (5.4% vs. 2.8%, $p = 0.150$) and composite endpoint (37.6% vs. 20.3%, $p < 0.001$) compared to younger controls. No significant difference was noted with regard to non-fatal myocardial infarction (0 vs. 0.9%, $p = 0.518$), target vessel revascularization (5.4% vs. 3.5%, $p = 0.242$) and ischemic stroke (6.7% vs. 4.7%, $p = 0.289$).

For very old patients, multivariate Cox regression revealed cardiac dysfunction (HR: 2.564, 95% CI: 1.279–5.139, $p = 0.008$), RD (HR: 4.001, 95% CI: 1.518–10.546, $p = 0.005$) and STEMI at presentation (HR: 2.529, 95% CI: 1.275–5.013, $p = 0.008$) as independ-

Table 1
Clinical characteristics at baseline according to presenting ages.

	Patients ≥ 80 years (n=164)	Patients between 65 and 79 years (n = 1340)	*p* value
Age (y)	82.5 ± 2.7	71.8 ± 4.1	< 0.001
Male/Female, n (%)	108 (65.9)/56 (34.1)	847 (63.2)/493 (36.8)	0.507
Hypertension, n (%)	128 (78.0)	1028 (76.7)	0.703
Diabetes, n (%)	58 (35.4)	417 (31.1)	0.269
Current smoker, n (%)	41 (25.0)	488 (36.4)	0.004
Previous MI, n (%)	7 (4.3)	48 (3.6)	0.659
Previous PCI, n (%)	40 (24.4)	256 (19.1)	0.108
Previous CABG, n (%)	4 (2.4)	53 (4.0)	0.337
Previous ischemic stroke, n (%)	27 (16.5)	227 (16.9)	0.878
Previous hemorrhagic stroke, n (%)	0 (0)	11 (0.8)	0.497
Previous gastrointestinal bleeding, n (%)	2 (1.2)	4 (0.3)	0.132
RD[a], n (%)	112 (68.3)	420 (31.3)	< 0.001
Anemia, n (%)	81 (49.4)	445 (33.2)	< 0.001
Hemoglobin (g/L)	125.6 ± 16.5	133.6 ± 17.6	< 0.001
Hematocrit (%)	37.6 ± 4.7	39.6 ± 4.8	< 0.001
STEMI, n (%)	36 (22.0)	168 (12.5)	0.001
Cardiac dysfunction[b], n (%)	60 (36.6)	376 (28.1)	0.023
Multivessel PCI, n (%)	34 (20.7)	303 (22.6)	0.586
Number of stents	1.72 ± 0.9	1.81 ± 1.0	0.273
Antithrombotic agents, n (%)			
Triple therapy[c]	4 (2.4)	57 (4.3)	0.266
Dual antiplatelet	157 (95.7)	1268 (94.6)	0.549
Single antiplatelet plus warfarin	3 (1.8)	15 (1.1)	0.683
β receptor blockers, n (%)	120 (73.2)	1004 (74.9)	0.625
ACEI/ARB, n (%)	83 (50.6)	817 (61.0)	0.011
Statins, n (%)	148 (90.2)	1257 (93.8)	0.082
PPI, n (%)	57 (34.8)	336 (25.1)	0.008

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor; RD, renal dysfunction; STEMI, ST segment elevation myocardial infarction.

[a] RD refers to creatinine clearance < 60 ml/min.

[b] Cardiac dysfunction refers to symptomatic heart failure or a reduced left ventricular ejection fraction of less than 50%.

[c] Dabigatran was used in one patient ≥ 80 years and one patient between 65 and 79 years; rivaroxaban was used in one patient between 65 and 79 years.

ent risk factors for all-cause death; cardiac dysfunction (HR: 2.590, 95% CI: 1.470–4.565, p = 0.001) and RD (HR: 4.204, 95% CI: 1.865–9.476, p = 0.001) as independent predictors for MACCE; cardiac dysfunction (HR: 2.417, 95% CI: 1.399–4.176, p = 0.002), RD (HR: 4.278, 95% CI: 1.997–9.164, p < 0.001) and STEMI at presentation (HR: 1.767, 95% CI: 1.008–3.097, p = 0.047) as independent risk factors for the composite endpoint (Table 2). Antithrombotic strategy did not have a significant influence on all cause death, MACCE or composite endpoint.

4. Discussion

In this multicenter observational study, we reviewed the clinical data of elderly patients with AF undergoing coronary stenting, and showed very old patients had distinct clinical characteristics with worse long-term clinical outcomes compared to younger patients. We also identified cardiac dysfunction and moderate-to-severe RD as independent risk factors for adverse cardiovascular events in very old patients.

Very old patients comprised 10.9% of the elderly population (≥ 65 years) with AF undergoing PCI in this study, compared to 26.3% in a retrospective analysis of Duke Clinical Research Institute.[7] In our study, very old patients had more age-related co-morbidities such as malnutrition, impaired cardiac and renal function. These conditions exerted an adverse impact on clinical outcomes in this population. Interestingly, the very old patients in this study had a lower prevalence of current smokers and no history of hemorrhagic stroke, reflecting the greater longevity in non-smokers and the reluctance of interventional cardiologists to treat octogenarians with high bleeding risk.

Previous studies showed elderly patients (≥ 65 years) with heart failure had a worse prognosis than younger adults, with 1-year mortality increasing linearly with age and reaching 39% in those 80 years or older.[8,9] Relative to those without AF, AF patients with coronary stenting often had an advanced age and were more likely to have congestive heart failure.[1,4] Cardiac dysfunction represented more than one-third of very old patients in this study, and was independently associated with occurrence of death (HR: 2.56) and MACCE (HR: 2.59).

RD has been recognized as a prognostic factor in acute coronary syndrome or after coronary stenting.[10–16] In our study, moderate-to-severe RD occurred in more than two-thirds of very old patients (relative to less than one-third of younger controls) and was associated with worsened cardiovascular outcomes. Similarly, RD was independently associated with 1-year all-cause mortality and MACCE in patients with AF referred for PCI in the AFCAS registry.[17] Several potential pathophysiological pathways have been proposed for the poor prognosis. RD induces thrombotic disorders, promotes inflammation, activates multiple neurohormonal signaling pathways (including sympathetic nervous system, rennin-angiotensin-aldosterone system, endothelin and vasopressin).[18] All these pathophysiologic changes worsen ischemia, myocardial dysfunction and end-organ injury.

DAPT was used predominantly (94.7%) in this elderly Chinese population irrespective of estimated thrombotic and bleeding risks. This proportion was similar but much more than that in the CRUSADE Registry, in which elderly patients (≥ 65 years) receiving triple therapy (27%) versus DAPT (73%) had a similar risk of an ischemic event but a trend toward increased bleeding.[19] The less use of triple therapy in this study reflected the concern from many Chinese cardiologists of excessive bleeding after coronary stenting when warfarin was used with antiplatelet agents. Actually, warfarin was underused in the general AF population in China. In a multicenter registry from 50 hospitals in China, 86.2% of patients with nonvalvular AF had $CHADS_2$ score ≥ 1, but only 42.6% were on warfarin.[20] The most common reasons were patient unwillingness to receive regular INR monitoring (43.0%) and high risk of bleeding (33.3%).[20] Randomized clinical trials in patients with nonvalvular AF have demonstrated that NOAC are noninferior or superior to warfarin in efficacy and safety. Some NOAC have also shown promise in preventing thrombotic events in patients with AF and coronary

Table 2
Univariate and multivariate Cox regression analysis of risk factors for adverse clinical outcomes.

	Death		MACCE		Composite Endpoint	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Male	1.093 (1.007–1.186)		1.052 (0.579–1.909)		1.308 (0.731–2.338)	
Hypertension	2.287 (0.804–6.505)		2.186 (0.930–5.134)		2.142 (0.969–4.733)	
Diabetes	1.284 (0.648–2.544)		1.400 (0.798–2.456)		1.350 (0.793–2.300)	
Previous MI	2.822 (0.858–9.284)		2.621 (0.935–7.345)		3.347 (1.316–8.513)	
Previous PCI	0.456 (0.161–1.295)		0.754 (0.366–1.553)		0.851 (0.440–1.646)	
Previous CABG	0.047 (0–454.9)		0.047 (0–70.784)		0.047 (0–43.871)	
Previous ischemic stroke	1.209 (0.500–2.924)		1.315 (0.657–2.631)		1.287 (0.665–2.490)	
Previous major bleeding	0.760 (0.103–5.582)		1.874 (0.581–6.041)		2.638 (0.945–7.365)	
RD[a]	3.013 (1.165–7.795)	4.001 (1.518–10.546)	3.366 (1.512–7.496)	4.204 (1.865–9.476)	3.396 (1.603–7.192)	4.278 (1.997–9.164)
Anemia	0.827 (0.420–1.628)		0.791 (0.452–1.384)		0.888 (0.525–1.503)	
STEMI at presentation	2.744 (1.393–5.408)	2.529 (1.275–5.013)	1.778 (0.988–3.200)		2.024 (1.169–3.504)	1.767 (1.008–3.097)
Cardiac dysfunction[b]	2.233 (1.137–4.386)	2.564 (1.279–5.139)	2.021 (1.159–3.526)	2.590 (1.470–4.565)	2.076 (1.227–3.512)	2.417 (1.399–4.176)
Multivessel PCI	0.361 (0.110–1.180)		0.755 (0.354–1.608)		0.640 (0.303–1.353)	
Number of stents	0.844 (0.568–1.254)		0.968 (0.721–1.301)		0.967 (0.732–1.277)	
Triple therapy	1.784 (0.241–13.186)		1.502 (0.206–10.947)		1.241 (0.171–9.013)	
Single antiplatelet plus warfarin	0.010 (0–998.2)		2.376 (0.325–17.368)		1.990 (0.274–14.485)	
β blockers	0.772 (0.369–1.616)		0.909 (0.483–1.713)		1.111 (0.597–2.068)	
ACEI/ARB	0.582 (0.294–1.154)		0.660 (0.377–1.154)		0.610 (0.359–1.038)	
Statins	0.555 (0.229–1.345)		0.534 (0.250–1.143)		0.633 (0.298–1.345)	
PPI	1.160 (0.573–2.349)		0.822 (0.448–1.508)		0.752 (0.420–1.344)	

Data were expressed as hazard ratio with 95% credential interval.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor; RD, renal dysfunction; STEMI, ST segment elevation myocardial infarction.
[a] RD refers to creatinine clearance < 60 ml/min.
[b] Cardiac dysfunction refers to symptomatic heart failure or a reduced left ventricular ejection fraction of less than 50%.

stenting.[21] However, NOAC were rarely used in our cohort, because they were expensive and not covered by the medical insurance system in Beijing during the study period. The choice for the superior antithrombotic strategy for patients with AF and coronary stenting remained controversial. The WOEST trial and some other large-scale observational studies favored clopidogrel plus warfarin due to a similar thrombotic risk and lower bleeding risk.[6,22] Unfortunately, patients older than 80 years were usually excluded from clinical trials. In this study, the small number of patients with antithrombotic therapy other than DAPT contributed at least partly to the lack of influence of antithrombotic strategy on clinical outcomes. As for those with triple therapy, none of the four very old patients had major bleeding as compared with 5.3% of patients in the control group. However, the small population with triple therapy rendered this comparison inaccurate and meaningless.

There are some limitations to this study. This study was not prospectively designed to assess the long-term prognosis of elderly patients with AF and coronary stenting, and the data utilized for analysis was derived from 12 hospitals in Beijing. As an inherent nature of retrospective studies, some demographic and clinical information may be missing, such as body mass index. As all studies involving multicenter databases and registries, there was no audit of data quality and precision. For patients who had lost contact, we looked up the national demographic registry to confirm whether they were dead or alive. However, the cause of death was missing, unclear or inaccurate for a considerable amount of patients in the demographic registry, and therefore we could not discriminate cardiac from non-cardiac death. All patients were treated with drug eluting stents, but the stents came from many different manufactures and were coated with different drugs, which confounded the 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.

In conclusion, patients 80 years or older with a history of AF undergoing coronary stenting had distinct clinical characteristics and doubled rates of all-cause death, MACCE and major bleeding compared with those between 64 and 79 years during a mean follow-up period of 39 months. Cardiac dysfunction and moderate-to-severe RD independently predicted adverse clinical outcomes in this very old population.

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Conflict of interest

None.

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