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), 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 more 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: 4.278, 95% CI: 1.997–9.164, p < 0.001), and STEMI (HR: 1.767, 95% CI: 1.470–2.127, p = 0.001) as independent predictors for all-cause death; cardiac dysfunction (HR: 2.590, 95% CI: 1.470–4.565, p = 0.001) and STEMI (HR: 2.417, 95% CI: 1.390–4.176, p = 0.002) as independent predictors for MACCE; cardiac dysfunction (HR: 2.417, 95% CI: 1.390–4.176, p = 0.002) and STEMI (HR: 2.417, 95% CI: 1.390–4.176, p = 0.002) as independent predictors for MACCE; cardiac dysfunction (HR: 2.564, 95% CI: 1.279–5.139, p = 0.008), RD (HR: 4.278, 95% CI: 1.997–9.164, p < 0.001), and STEMI (HR: 1.767, 95% CI: 1.470–2.127, p = 0.001) 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.

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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).
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, χ2 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 CHA2DS2-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 independent predictors of death (HR: 2.718, 95% CI: 1.766–4.101, p < 0.001), MACCE (33.6% vs. 18.5% 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).
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.5 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 AFACAS 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 pathophysiological 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 CHADS2 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.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Death Univariate</th>
<th>Multivariate</th>
<th>MACCE Univariate</th>
<th>Multivariate</th>
<th>Composite Endpoint Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.093 (1.007–1.186)</td>
<td>1.052 (0.579–1.909)</td>
<td>1.308 (0.731–2.338)</td>
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<tr>
<td>Hypertension</td>
<td>2.287 (0.804–6.050)</td>
<td>2.186 (0.930–5.134)</td>
<td>2.142 (0.969–4.733)</td>
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<tr>
<td>Diabetes</td>
<td>1.284 (0.648–2.544)</td>
<td>1.400 (0.798–2.456)</td>
<td>1.350 (0.793–2.300)</td>
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<tr>
<td>Previous MI</td>
<td>2.822 (0.858–9.284)</td>
<td>2.621 (0.935–7.345)</td>
<td>3.347 (1.316–8.513)</td>
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<tr>
<td>Previous PCI</td>
<td>0.456 (0.161–1.295)</td>
<td>0.754 (0.366–1.553)</td>
<td>0.851 (0.440–1.646)</td>
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<tr>
<td>Previous CABG</td>
<td>0.047 (0–454.9)</td>
<td>0.047 (0–70.784)</td>
<td>0.047 (0–43.871)</td>
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<tr>
<td>Previous ischemic stroke</td>
<td>1.209 (0.500–2.924)</td>
<td>1.315 (0.657–2.631)</td>
<td>1.287 (0.665–2.490)</td>
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<tr>
<td>Previous major bleeding RD</td>
<td>0.760 (0.103–5.582)</td>
<td>1.874 (0.581–6.041)</td>
<td>2.638 (0.945–7.365)</td>
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<tr>
<td>Anemia</td>
<td>0.827 (0.420–1.628)</td>
<td>0.791 (0.452–1.384)</td>
<td>0.888 (0.525–1.503)</td>
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<tr>
<td>STEMI at presentation</td>
<td>2.744 (1.393–5.408)</td>
<td>2.529 (1.275–5.013)</td>
<td>2.024 (1.169–3.504)</td>
<td>1.767 (1.008–3.097)</td>
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<tr>
<td>Cardiac dysfunction</td>
<td>2.233 (1.137–4.386)</td>
<td>2.021 (1.159–3.526)</td>
<td>2.076 (1.227–3.512)</td>
<td>2.417 (1.399–4.76)</td>
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<tr>
<td>Multivessel PCI</td>
<td>0.361 (0.111–1.180)</td>
<td>0.755 (0.354–1.608)</td>
<td>0.640 (0.303–1.353)</td>
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<tr>
<td>Number of stents</td>
<td>0.844 (0.568–1.254)</td>
<td>0.968 (0.721–1.301)</td>
<td>0.967 (0.732–1.277)</td>
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<tr>
<td>Triple therapy</td>
<td>1.784 (0.241–13.186)</td>
<td>1.502 (0.206–10.947)</td>
<td>1.241 (0.171–9.013)</td>
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<tr>
<td>Single antiplatelet plus warfarin</td>
<td>0.010 (0–998.2)</td>
<td>2.376 (0.325–17.368)</td>
<td>1.990 (0.274–14.485)</td>
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<tr>
<td>( \beta ) blockers</td>
<td>0.772 (0.369–1.616)</td>
<td>0.909 (0.483–1.713)</td>
<td>1.111 (0.597–2.068)</td>
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<tr>
<td>ACEI/ARB</td>
<td>0.582 (0.294–1.154)</td>
<td>0.660 (0.377–1.154)</td>
<td>0.610 (0.359–1.038)</td>
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<tr>
<td>Statins</td>
<td>0.555 (0.229–1.345)</td>
<td>0.534 (0.250–1.134)</td>
<td>0.633 (0.298–1.345)</td>
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<tr>
<td>PPI</td>
<td>1.160 (0.573–2.349)</td>
<td>0.822 (0.448–1.508)</td>
<td>0.752 (0.420–1.344)</td>
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</tbody>
</table>

Data were expressed as hazard ratio with 95% confidential 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.

\( \beta \) RD refers to creatinine clearance < 60 ml/min.

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