Sex Differences in Long-Term Clinical Outcomes in Patients With Atrial Fibrillation Undergoing Coronary Stent Implantation

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Background: Patients with concomitant atrial fibrillation (AF) and coronary stenting are at high risk for both cardiovascular and bleeding events. We aimed to evaluate the influence of sex on long-term clinical outcomes in this patient subset.

Methods and Results: We identified 1,450 patients with AF and coronary stenting in a patient-level pooled database from 3 Japanese studies, and compared 3-year clinical outcomes between men and women (n=1,075, and n=375, respectively). The cumulative 3-year incidence of all-cause death was significantly higher in women than in men (26.5% vs. 17.2%, log-rank P<0.001), although after adjusting for confounders, the excess mortality risk of women relative to men was no longer significant (hazard ratio (HR): 1.12, 95% confidence interval (CI): 0.85–1.46, P=0.42). There were no significant differences in the adjusted 3-year risks for myocardial infarction or stroke between men and women (HR: 1.25, 95% CI: 0.62–2.40, P=0.52, and HR: 1.15, 95% CI: 0.75–1.74, P=0.52, respectively). However, both the cumulative 3-year incidence of and adjusted risk for major bleeding were significantly higher in women than in men (17.0% vs. 11.3%, log-rank P=0.002, and HR: 1.47, 95% CI: 1.03–2.07, P=0.03).

Conclusions: Among patients with concomitant AF and coronary stenting, there were no significant differences in the adjusted 3-year risks for all-cause death, myocardial infarction, and stroke between men and women. However, women as compared with men were associated with excess adjusted risk for major bleeding.

Key Words: Atrial fibrillation; Coronary artery disease; Outcomes; Sex

Patients with atrial fibrillation (AF) who have undergone percutaneous coronary intervention (PCI) using coronary stents are known to be at high risk for both cardiovascular and bleeding events. Optimal antithrombotic therapy for those patients is still under debate. The influence of sex difference on clinical outcomes in cardiovascular disease is also controversial.

Most previous studies in patients with coronary artery disease (CAD) have reported that women had significantly higher observed mortality rates than men. However, there are conflicting reports regarding the higher mortality risk of women relative to men after adjusting for age and comorbidities. Several studies have reported that among AF patients women as compared with men were associated with significantly higher risk for stroke, but not for death. However, there is no previous study evaluating the influence of sex on long-term clinical outcomes in this patient subset.

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patients with concomitant AF and coronary stenting. Therefore, we sought to evaluate the influence of sex on the long-term clinical outcomes of AF patients who underwent PCI with coronary stenting in a large pooled cohort from 3 Japanese studies.

Methods

Study Population
We constructed a patient-level pooled database of 22,386 patients from 3 Japanese coronary revascularization studies conducted by the same group of investigators: the Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG (coronary artery bypass grafting) registry cohort-2, n=15,939; Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial (RESET), n=3,206; and NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT), n=3,241. The study designs and main results of the 3 studies have been published and are summarized in Table S1. Briefly, the CREDO-Kyoto registry cohort-2 was a multicenter observational registry that enrolled consecutive patients undergoing their first coronary revascularization (January 2005–December 2007). RESET was a randomized controlled trial (RCT) that compared sirolimus-eluting stent (SES) with everolimus-eluting stent (EES) without any exclusion criteria (February–July 2010). NEXT was a RCT that compared EES with biolimus-eluting stent (BES) without any exclusion criteria (May–October 2011). The follow-up duration was 5 years in the CREDO-Kyoto PCI/CABG registry cohort-2, and 3 years in RESET and NEXT. For the present analysis, the follow-up period was truncated at 3 years to standardize the follow-up duration.

Among the 22,386 patients in this pooled cohort, we identified 18,580 CAD patients who underwent PCI with stent implantation after excluding 2,782 patients with CABG, 909 patients who had PCI without stent implantation, 114 patients who refused study participation and 1 patient with duplicate enrollment. There were 1,450 (7.8%) patients with concomitant AF, who constituted the current study population (men: n=1,075; women: n=375) (Figure 1).

Definitions and Endpoints
Baseline clinical characteristics, such as hypertension, current smoking, heart failure (HF), prior myocardial infarction (MI) and malignancy, were regarded as present when these diagnoses were recorded in hospital charts. Elderly patients were defined as ≥75 years of age. Diabetes was defined as treatment with oral hypoglycemic agents and/or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥6.5%, or blood glucose level 200 mg/dL. Prior stroke was defined as ischemic or hemorrhagic stroke, including both symptomatic and asymptomatic stroke, detected by noninvasive imaging modalities. Peripheral vascular disease was regarded to be present when carotid, aortic, or other peripheral vascular disease was being treated or scheduled for surgical or endovascular intervention.
The outcome measures in the current analyses included all-cause death, cardiac death, non-cardiac death, MI, definite stent thrombosis (ST), stroke, hospitalization for HF, major bleeding, and any coronary revascularization. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Any death during the index hospitalization.

Table 1. Baseline Characteristics of the Study Patients With Concomitant AF and Coronary Stenting

| Variables | Total (n=1,450) | Men (n=1,075) | Women (n=375) | P value |
|-----------|----------------|---------------|---------------|---------|
| **Clinical characteristics** | | | | |
| Age, years | 72.8±8.9 | 71.4±8.8 | 76.8±8.0 | <0.001 |
| ≥75 years* | 662 (45.7) | 423 (39.4) | 239 (63.7) | <0.001 |
| BMI <25.0 kg/m2 * | 1,028 (70.9) | 753 (70.1) | 275 (73.3) | 0.23 |
| STEMI* | 325 (22.4) | 221 (20.6) | 104 (27.7) | 0.005 |
| Hypertension | 1,244 (85.8) | 922 (85.8) | 322 (85.9) | 0.96 |
| Diabetes mellitus* | 549 (37.9) | 398 (37.0) | 151 (40.3) | 0.27 |
| DM on insulin therapy | 110 (7.6) | 72 (6.7) | 38 (10.1) | 0.04 |
| Current smoking* | 282 (19.4) | 261 (24.3) | 21 (5.6) | <0.001 |
| HF* | 566 (39.0) | 391 (36.4) | 175 (46.7) | <0.001 |
| LVEF ≤40% | 196 (15.6) | 155 (16.6) | 41 (12.6) | 0.08 |
| Prior MI* | 256 (17.7) | 197 (18.3) | 59 (15.7) | 0.25 |
| Prior stroke* | 267 (18.4) | 198 (18.4) | 69 (18.4) | 0.99 |
| Peripheral vascular disease* | 130 (9.0) | 107 (10.0) | 23 (6.1) | 0.02 |
| eGFR <30 mL/min/1.73 m², without HD* | 83 (5.7) | 47 (4.4) | 36 (9.6) | <0.001 |
| HD* | 84 (5.8) | 56 (5.2) | 28 (7.5) | 0.12 |
| Anemia (Hb <11 g/dL)* | 224 (15.4) | 125 (11.6) | 99 (26.4) | <0.001 |
| Malignancy* | 139 (9.6) | 107 (10.0) | 32 (8.5) | 0.42 |
| Paroxysmal AF | 864 (64.5) | 630 (62.5) | 234 (67.0) | 0.008 |
| CHADS2 score | 4.0±1.7 | 3.8±1.6 | 5.2±1.4 | <0.001 |
| CHA2DS2-VASc score | 2.4±1.2 | 2.3±1.3 | 2.7±1.2 | <0.001 |
| High (≥2) | 1,378 (95.0) | 1,003 (93.3) | 375 (100) | <0.001 |
| **Procedural characteristics** | | | | |
| No. of target lesions | 1 (1–2) | 1 (1–2) | 1 (1–2) | 0.41 |
| Target of unprotected LMCA | 66 (4.6) | 48 (4.5) | 18 (4.8) | 0.79 |
| Target of proximal LAD* | 785 (54.1) | 581 (54.1) | 204 (54.4) | 0.91 |
| Target of CTO | 134 (9.2) | 99 (9.2) | 35 (9.3) | 0.94 |
| Use of DES | 961 (66.2) | 723 (67.3) | 238 (63.5) | 0.18 |
| 1st-generation DES* | 634 (43.7) | 456 (42.4) | 178 (47.5) | 0.09 |
| 2nd-generation DES* | 333 (23.0) | 270 (25.1) | 63 (16.8) | <0.001 |
| Total stent length, mm | 28 (18–44) | 28 (18–43) | 28 (18–46) | 0.35 |
| **Medications at hospital discharge** | | | | |
| Antiplatelet therapy | | | | |
| Thienopyridine | 1,430 (98.6) | 1,062 (98.8) | 368 (98.1) | 0.36 |
| Aspirin | 1,427 (98.4) | 1,061 (98.7) | 366 (97.6) | 0.16 |
| Cilostazol | 218 (15.0) | 165 (15.4) | 53 (14.1) | 0.57 |
| Other medications | | | | |
| Statins* | 694 (47.9) | 511 (47.5) | 183 (48.8) | 0.67 |
| β-blockers* | 595 (41.0) | 446 (41.5) | 149 (39.7) | 0.55 |
| ACEI/ARB* | 898 (61.9) | 663 (61.7) | 235 (62.7) | 0.73 |
| Nitrates | 431 (29.7) | 309 (28.7) | 122 (32.5) | 0.17 |
| CCBs | 622 (42.9) | 461 (42.9) | 161 (42.9) | 0.99 |
| Warfarin* | 703 (48.5) | 558 (51.9) | 145 (38.7) | <0.001 |

Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Patients with LVEF <40% were regarded as having LV dysfunction. Anemia was defined as blood hemoglobin level <11.0 g/dL. Baseline medications were regarded as present if prescribed during the index hospitalization.
Sex Differences in Outcomes in AF and CAD

Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. The effects of women relative to men for the individual endpoints were expressed as hazard ratios (HR) and their 95% confidence intervals (CI). We estimated the HR by Cox proportional hazard models adjusting for 19 clinically relevant factors listed in Table 1. Continuous variables were dichotomized by clinically meaningful reference values or median values. Proportional hazard assumptions for potential independent risk-adjusting variables were assessed on the plots of log (time) vs. log [-log (survival)] stratified by the variable, and the assumptions were verified to be acceptable for all the variables.

To assess the different effect of sex difference on the risks for death and major bleeding, we also conducted landmark analyses at 30 days after the index PCI.

All statistical analyses were conducted using JMP 12.0 software (SAS Institute Inc., Cary, NC, USA). All reported
and 4.0±1.7, respectively. The prevalence of CHA2DS2-VASc score ≥2 was 95.0% (Figure 2). Warfarin was prescribed only in 48.5% of patients; aspirin and thienopyridine were prescribed in the vast majority of patients.

There were several important differences between men and women in the baseline clinical characteristics. Women as compared with men were older and more often had ST-segment elevation MI presentation, insulin-treated diabetes mellitus, HF, renal dysfunction without hemodialysis, and

Results

Baseline Characteristics

The current study population included a large proportion of patients with advanced age and comorbidities (Table 1). Mean CHADS2 and CHA2DS2-VASc scores were 2.4±1.2 and 4.0±1.7, respectively. The prevalence of CHA2DS2-VASc score ≥2 was 95.0% (Figure 2). Warfarin was prescribed only in 48.5% of patients; aspirin and thienopyridine were prescribed in the vast majority of patients.

There were several important differences between men and women in the baseline clinical characteristics. Women as compared with men were older and more often had ST-segment elevation MI presentation, insulin-treated diabetes mellitus, HF, renal dysfunction without hemodialysis, and

Figure 3. (A–D) Cumulative incidences of clinical outcome measures for all-cause death, myocardial infarction (MI), stroke and major bleeding through 3-year follow-up: men vs. women.
Long-Term Clinical Outcomes in Men and Women

The cumulative 3-year incidence of all-cause death was significantly higher in women than in men (26.5% vs. 17.2%, log-rank P<0.001) (Figure 3). After adjusting for confounders, the excess mortality risk of women relative to men was no longer significant (HR: 1.12, 95% CI: 0.85–1.46, P=0.29; 37.6% vs. 38.0%, P=0.91, respectively). The excess adjusted risk of women relative to men for mortality within and beyond 30 days after the index coronary stent implantation (4.8% vs. 2.4%, log-rank P=0.03) was no longer significant (HR: 1.46, 95% CI: 0.72–2.22, P=0.09; 1.24, 95% CI: 0.77–1.96, P=0.37). The cumulative 3-year incidence of any coronary revascularization (4.6% vs. 1.2%, log-rank P=0.003), but not significantly different between men and women beyond 30 days (8.4% vs. 10.3%, log-rank P=0.26; HR: 1.17, 95% CI: 0.74–1.81, P=0.50) (Figure S1, Table S2).

The cumulative 3-year incidence of any coronary revascularization tended to be lower in women than in men, and there was a borderline significant difference in the adjusted risk for any coronary revascularization between men and women (24.6% vs. 19.5%, log-rank P=0.08; HR: 0.75, 95% CI: 0.56–0.96, P=0.047).

The prescription rates of DAPT at hospital discharge, 1-year and 3-year follow-up were 97.4%, 57.3% and 37.7%, respectively, and were not significantly different between men and women (97.7% vs. 96.5%, P=0.25, 58.1% vs. 54.9%, P=0.31; 37.6% vs. 38.0%, P=0.91, respectively).

Discussion

The main findings of the current study evaluating the sex differences in AF patients undergoing coronary stenting were as follows: (1) women as compared with men more often had high-risk features such as advanced age, insulin-treated diabetes mellitus, renal failure, HF, anemia, and higher CHA2DS2-VASc score; (2) OACs were less often prescribed in women than in men despite their high risk for thromboembolic events; (3) there were no significant differences in the adjusted 3-year risks for all-cause death, MI, and stroke between men and women, but women as compared with men were associated with excess adjusted risk for major bleeding. AF was present in 7.8% of CAD patients who underwent PCI with stent implantation in the current study, which was consistent with previous Japanese studies.6,28 Those CAD patients with AF were a higher risk population for both cardiovascular and bleeding events as compared with those without AF.1,12 Recent clinical trials have evaluated various antithrombotic regimens in this patient subset with concomitant AF and coronary stenting.3,4,6,28 The WOEST (What is the Optimal anti-platelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) and PIONEER studies.
AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) studies have demonstrated significant reductions of bleeding events by the combination of OAC and P2Y12 inhibitor without aspirin as compared with the triple therapy of OAC and DAPT.4,5 Reflecting these results, current clinical guidelines recommend a short duration of triple or dual therapy with OAC and P2Y12 inhibitor without aspirin in patients with concomitant AF and coronary stenting.6,7 The current study clearly showed that the majority of patients with concomitant AF and coronary stenting had high risk of thromboembolic events requiring OAC, supporting the current guidelines recommendations of emphasizing OAC rather than DAPT. More recently, the RE-DUAL PCI (Randomized Evaluation of Dual Anti-thrombotic Therapy with Darabigatan vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial demonstrated that even a very short duration of triple therapy with warfarin and DAPT (1 month after bare-metal stents and 3 months after drug-eluting stents) was still associated with a significantly higher risk for bleeding than dual therapy with dabigatran and P2Y12 inhibitor.8

Regarding the sex differences in patients with concomitant AF and coronary stenting, women were much older and more often had serious comorbidities such as renal failure, HF, and anemia. Advanced age and these comorbidities are not only risk factors for thromboembolic events, but also for bleeding events. Concerns about bleeding might have led to less frequent warfarin use in women than in men, which could predispose them to the increased incidence of thromboembolic events. Regarding the long-term clinical outcomes, there were no significant differences in the adjusted risks for all-cause death, MI, and stroke between men and women. Therefore, female sex itself might not be related to the increased risk for cardiovascular events in patients with concomitant AF and coronary stenting. However, even if statistically not significant, women as compared with men had a numerically higher adjusted risk for all-cause death, MI, and stroke. Considering the limited sample size of the present study, we could not deny the possibility of a modestly higher risk of women relative to men for cardiovascular events. There are many possible mechanisms for the sex-related difference in the risk for cardiovascular events, including genetically different response to anticoagulation therapy, vascular physiology, influence of sex hormones, and different behavior regarding medical therapy.3,9 Therefore, future larger studies are required to investigate the influence of sex on cardiovascular events in patients with concomitant AF and coronary stenting. Furthermore, women as compared with men were associated with significantly higher risk for bleeding. It also should be noted that the excess bleeding risk of women was seen within 30 days after the index coronary stent implantation, when the vast majority of patients were treated by either triple therapy or DAPT. Indeed, it was reported that female sex was an independent predictor of major bleeding within 30 days after PCI, which was strongly associated with an increased risk of subsequent death at 1 year.33 Among patients with AF receiving vitamin K antagonists, women as compared with men were associated with higher risk for bleeding in the CARAF (Canadian Registry of Atrial Fibrillation) study,34 and in a retrospective cohort analysis from Medicare’s National Stroke Project.35 Furthermore, among patients undergoing PCI, women were also associated with higher risk for major bleeding in the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) registry,36 and TRITON-TIMI 38 (Thrombolysis in Myocardial Infarction 38) studies.37 Avoiding bleeding events might be an important consideration, particularly for women, when receiving intensive antithrombotic therapy. According to meta-analyses of DAPT after drug-eluting stent implantation, bleeding was associated with non-cardiovascular death, whereas ST was not associated with cardiovascular death.38 It appears important to recognize that female patients with concomitant AF and coronary stenting may have high-risk features such as advanced age and severe comorbidities, and thus are at high risk for cardiovascular and bleeding events.

Study Limitations
First, despite the appropriate statistical adjustment for potential confounders, residual confounding factors might have affected the results of the current study. Second, we had no data about bleeding classification according to the Thrombosis in Myocardial Infarction (TIMI) criteria in the CREDO-Kyoto PCI/CABG registry cohort-2, and no data about bleeding classification according to the International Society on Thrombosis and Haemostasis (ISTH) and Bleeding Academic Research Consortium (BARC) criteria in all 3 studies included in this pooled analysis. The evaluation using different bleeding classifications such as the ISTH and BARC criteria might influence the results of this study. Third, the prescription rates of evidence-based medicines such as statins and β-blockers in this study were low according to the current standard, especially in the CREDO-Kyoto registry cohort-2 in which patients were enrolled between January 2005 and December 2007. Fourth, all the studies were conducted before the introduction of non-vitamin K OACs (NOACs) in Japan. The introduction of NOACs would have improved the prescription rate of OACs, especially in women, and might have influenced the relative clinical outcomes between women and men.13 Finally, we could not obtain information on the status of OAC prescription after hospital discharge, and time in therapeutic range for patients receiving warfarin, and therefore we could not evaluate different intensity of OAC therapies on clinical outcomes in the current study.

Conclusions
Among patients with concomitant AF and coronary stenting, there were no significant differences in the adjusted 3-year risks for all-cause death, MI, and stroke between men and women, although the women were older and more often had serious comorbidities than the men. Women as compared with men were associated with excess adjusted risk for major bleeding.

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Sex Differences in Outcomes in AF and CAD

Disclosures
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### Supplementary Files

**Supplementary File 1**

**Appendix S1. List of Clinical Research Coordinators**

**Figure S1.** Landmark analyses (cumulative incidence curves) of (A) all-cause death and (B) major bleeding at 30 days: men vs. women.

**Table S1.** Designs and results of the 3 contributory studies, and baseline characteristics of the current study population

**Table S2.** Crude and adjusted risks for all-cause death and major bleeding within and beyond 30 days: men vs. women

Please find supplementary file(s):
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