Is Female Sex Always a Risk for Bleeding?

Hidehira Fukaya, MD, PhD; Junya Ako, MD, PhD

Sex-related differences in cardiovascular outcomes have long been recognized. In the field of interventional cardiology, it is well known that women as compared with men have a higher risk of bleeding complications during and after percutaneous coronary intervention (PCI).

Regarding the periprocedural adverse events of coronary stenting and short-term mortality rates, previous studies have clearly shown that women have a higher risk of bleeding complications (Table) and a higher mortality rate, but the long-term outcomes in these patients have not been fully determined. Female sex has been reported as

### Table. Studies Focusing on Sex Differences Regarding Bleeding Complications in AF Patients Undergoing Coronary Stenting

| Authors        | Ethnicity | Year published | Data source                                      | Patient no. total/female | Observation period (years) | Major bleeding event OR/HR (95% CI) | Thromboembolic event OR/HR (95% CI) |
|----------------|-----------|----------------|--------------------------------------------------|--------------------------|---------------------------|-------------------------------------|-------------------------------------|
| PCI            |           |                |                                                  |                          |                           |                                     |                                     |
| Feit et al     | Worldwide | 2007           | REPLACE-2 trial                                  | 6,001/1,537              | 1                         | OR 1.54 (1.12–2.10)               | NA                                  |
| Akhter et al   | USA       | 2009           | American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) | 199,690/68,026           | NA only evaluated in periprocedural period | OR 0.55 (0.52–0.58, P<0.01) | NA                                  |
| Pemdyala et al | USA       | 2013           | Retrospective registry                           | 6,929/2,474              | 1                         | In-hospital major bleeding W vs. M=3.2% vs. 2.8%, P=0.364 | In-hospital stroke W vs. M=0.7% vs. 0.3%, P=0.023 |
| Park et al     | Korea     | 2014           | Meta-analysis of 11 prospective studies          | 23,604/7,180             | 2.1                       | 30-day HR 1.92 (1.31–2.81, P<0.001) | 30-day HR 1.01 (0.50–2.41, P=0.81) |
| Numasawa et al | Japan     | 2017           | Nationwide J-PCI registry                        | 43,239/11,326            | 1                         | OR 1.94 (1.35–2.79)               | NA                                  |
| AF             |           |                |                                                  |                          |                           |                                     |                                     |
| Lip et al      | 35 country in Europe | 2010 | Euro Heart Survey                              | 1,084/442                | 1                         | NA                                  | OR 2.53 (1.08–5.92, P=0.029) |
| Suzuki et al   | Japan     | 2015           | Pooled analysis of registries                    | 3588/1,216               | 1.4                       | NA                                  | NS: HR 1.07 (0.65–1.76)            |
| Renoux et al   | Canada    | 2017           | RAMQ (Reie de l’assurance maladie du Quebec)    | 147,662/76,487           | 2.9                       | Adjusted HR 0.91 (0.88–0.95) Time-dependent adjustment RR 0.85 (0.82–0.88) | Adjusted HR 1.16 (1.11–1.21) Time-dependent adjustment RR 1.01 (0.97–1.05) |
| PCI with AF    |           |                |                                                  |                          |                           |                                     |                                     |
| Matsumura-Nakano et al | Japan | 2018           | CREDO-Kyoto PCI/CABG registry cohort-2, RESET, and NEXT | 1,450/375                | 3                         | HR 1.47 (1.03–2.07, P=0.03)       | HR 1.25 (0.62–2.40, P=0.52)       |

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; NA, not applicable; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; RR, rate ratio.

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Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

Mailing address: Junya Ako, MD, PhD, Professor and Chairman, Department Cardiovascular Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara 252-0374, Japan. E-mail: jako@kitasato-u.ac.jp

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a thromboembolic risk in patients with atrial fibrillation (AF) rather than a bleeding risk, which is incorporated as the sex-category (Sc) in the CHA2DS-VASc scoring system. Therefore, female sex may be related with higher thromboembolic and bleeding risks in patients with AF who are undergoing coronary stenting.

In this issue of the Journal, Matsumura-Nakano et al. evaluate sex-related differences in the long-term outcomes of AF patients undergoing PCI. They extracted the data from 3 large Japanese cohorts with a study population of 1,450 patients with AF and coronary stenting. Women in this study were older, had more comorbidities, and higher CHA2DS-VASc score compared with men. The cumulative 3-year incidence of major bleeding was significantly higher in women compared with men (17.0% vs. 11.3%, P=0.002), even after adjusting for confounders (hazard ratio (HR): 1.47, 95% confidence interval (CI): 1.0–2.07, P=0.03), while all-cause death, myocardial infarction and stroke were not significantly different between the sexes. Therefore, the authors conclude that women undergoing coronary stent implantation concomitant with AF show a higher adjusted risk for major bleeding events.

The important finding of this study is that female sex was associated with a higher bleeding complication rate compared with men over a relatively longer observation period, even after adjusted cofounders. However, caution should be exercised when interpreting this main result. Despite the stated conclusion, the clear difference in bleeding complications was seen within 30 days after PCI by landmark analyses. Importantly, thereafter there was minimal, if any, difference between the sexes in bleeding complications. The overall difference in bleeding was mostly driven by this initial difference.

Let us take a look at the other side of the equation: thromboembolic events. In contemporary clinical practice, is female sex really a risk for thromboembolism in AF patients? In a recent paper from Canada, sex difference became insignificant after matching for age and time-dependent adjustment for confounders (rate ratio: 1.01, 95% CI: 0.97–1.05), although women had a higher risk for ischemic stroke than men (HR: 1.16, 95% CI: 1.11–1.21) in the crude analysis. More recently, Nielsen et al reported that female sex was a risk modifier rather than a risk factor for stroke in AF. Japanese data also showed no significant difference between the sexes. For instance, Okumura et al reported that female sex was not a risk of ischemic stroke in the J-RHYTHM Registry, and Suzuki et al also showed that female sex was not a risk of thromboembolic events (HR: 1.07, 95% CI: 0.65–1.76, NS, Table). This present study confirms the recent findings that female sex itself may not be a risk for thromboembolic risk in patients receiving both anticoagulation and antiplatelet therapies. Taken together with the similar bleeding risk in the chronic phase shown in this study, we may not have to change our long-term treatment regimen according to the patient’s sex, which is in line with the current European Society of Cardiology guidelines recommending similar type and duration of dual antiplatelet therapy (DAPT) for females.

In this report, warfarin was the only available oral anticoagulant at the time the studies were performed. Currently, however, direct oral anticoagulants (DOACs) are being increasingly used for the prevention for thromboembolic events in AF patients, changing the clinical landscape of treatment of AF. Optimal antithrombotic therapy for AF patients undergoing PCI is still under debate. Several large clinical trials have just reported seeking optimal antithrombotic strategies for these patients to reduce thromboembolic and bleeding events. Triple therapy (i.e., DAPT with oral anticoagulants) is getting out of fashion, and fewer medications and a shorter period of multiple antithrombotic therapy are recommended in the guidelines. Sex differences in antithrombotic therapy will have to be reassessed in the near future, taking into account of these changes in clinical circumstances.

It has long been recognized that sex differences are an important issue in cardiology; however, there has been a paucity of data from Japan. In this regard, the data presented in this issue of the Journal are clinical important for guiding our clinical judgment. Clinicians should be aware of the higher risk of periprocedural bleeding complications in women with AF and coronary stenting. However, for the long-term treatment of such patients, further studies are still necessary to clarify the sex-related differences.

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Sex Differences in AF Undergoing PCI

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