Sex Differences in the Clinical Outcomes of Oral Anticoagulants in Patients with Atrial Fibrillation

Running Title: Sex Differences in Outcomes of Anticoagulants

Sharon W. Y. Law, MPharm,[a] Wallis C. Y. Lau, PhD,[a,b] Ian C. K. Wong, PhD,[a,b] Gregory Y. H. Lip, MD,[c,d] Michael T. Mok, FRACP,[e,f] Chung-Wah Siu, MD,[g] Esther W. Chan, PhD[a]

From the [a]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [b]Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom; [c]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; [d]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [e]Department of Cardiology, University Hospital Geelong, Geelong, Australia; [f]School of Medicine, Deakin University, Geelong, Australia; and the [g]Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China

Disclosures:
Dr. Chan has received research funding from The Hong Kong Research Grants Council, The Hong Kong Health and Medical Research Fund, Bristol-Myers Squibb, Pfizer and Janssen, a Division of Johnson & Johnson. Dr. Wong has received research funding from The Hong Kong Research Grants Council, The Hong Kong Health and Medical Research Fund, Bristol-Myers Squibb, Pfizer and Janssen, a Division of Johnson & Johnson. Dr. Lip reports provision of consultancy services for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo; and speaker's bureau services for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No disclosure was reported by other authors.

Address for Correspondence:
Dr. Esther W. Chan
Centre for Safe Medication Practice and Research,
Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine,
The University of Hong Kong,
Office 02-08, 2/F Laboratory Block, 21 Sassoon Road, Hong Kong SAR, China
Telephone: +852 2831 5110
Fax: +852 2817 0859
Email: ewchan@hku.hk.

Abstract
Background: Women with atrial fibrillation (AF) are at a higher risk of stroke, despite treatment with warfarin. It is unclear if women treated with non-vitamin K antagonist oral anticoagulants (NOACs) have better clinical outcomes, especially when considering the quality of anticoagulation control of warfarin.
Objectives: This study compared the effectiveness and safety outcomes of NOACs versus warfarin in men and women with stratifications for anticoagulation control.
Methods: Patients newly diagnosed with AF and prescribed oral anticoagulants during 2010-2015 were identified using the Hong Kong clinical database. Propensity score matching was performed in men and women separately. Further analysis was conducted to stratify warfarin users according to their anticoagulation control. Cox regression was used to compare the risk of ischemic stroke/systemic embolism (SSE), intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality in the specific sex.
Results: There were 4,972 men and 4,834 women successfully matched in our cohort. Compared to warfarin, NOAC use was associated with a lower risk of ICH (hazard ratio [HR]: 0.16; 95% confidence interval [CI]: 0.06 to 0.40) and all-cause mortality (HR: 0.55; 95% CI: 0.39 to 0.77) in women but not in men. The treatment by sex interaction was significant for ICH only, and a significantly lower risk of ICH remained in the NOAC group when compared to warfarin users with good anticoagulation control (HR: 0.13; 95% CI: 0.02 to 1.00) among women only. The risks of SSE and GIB with NOACs versus warfarin were comparable in both sexes.
Conclusions: NOACs were associated with a lower risk of ICH and all-cause mortality in women only, where the association of lower ICH risk remained when compared to warfarin users with good anticoagulation control.

Condensed Abstract: Women with atrial fibrillation are at a higher risk of stroke, despite treatment with warfarin. With the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), it remains unclear if women treated with NOACs have better clinical outcomes. When compared to warfarin, NOAC use was associated with a lower risk of intracranial hemorrhage and all-cause mortality in women, but this association was not observed in men. After stratification by anticoagulation control of warfarin, the association of a lower risk of intracranial hemorrhage remained in women only when comparing NOAC users to warfarin users with good anticoagulation control.

Key Words: Anticoagulant, sex difference, atrial fibrillation, female, intracranial hemorrhage, stroke

Abbreviations List
AF = Atrial fibrillation
TTR = Time in therapeutic range
NOAC = non-vitamin K antagonist oral anticoagulant
CDARS = Clinical Data Analysis and Reporting System
ICH = Intracranial hemorrhage
GIB = Gastrointestinal bleeding
SSE = Ischemic stroke/systemic embolism
HR = Hazard ratio
CI = Confidence interval
INR = International normalized ratio

Introduction

Atrial fibrillation (AF) is a global health concern with its growing prevalence, increase in healthcare burden, and significant morbidity and mortality (1,2). Patients with AF are five times more likely to have a stroke (3); and hence, oral anticoagulants are recommended for high-risk patients as thromboprophylaxis (4,5). However, the risk of stroke may be heterogeneous between men and women (6-9), raising the possibility of sex-specific anticoagulation management amongst patients with AF.

Although epidemiological data demonstrated that men have a higher risk of AF when compared to women, women with AF have a higher risk of stroke (1,2). In particular, female sex was identified as an independent risk factor for stroke in patients with AF even after adjustment for age (10). This is reflected in the female sex component in the CHA_2DS_2-VASc score for stroke risk prediction (11). Worse clinical outcomes of stroke were also found to be associated with women who are diagnosed with AF (12). Notably, the higher risk of stroke in women remained in the anticoagulated cohort where warfarin, a vitamin K antagonist, was prescribed (13).

It has been proposed that the worse clinical outcomes of women on warfarin may be due to their poor anticoagulation control as indicated in the low percentage time in therapeutic range (TTR) (14,15). With the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), it is uncertain whether women have better clinical outcomes when they are prescribed the newer agents which have a different mechanism of action. There is limited real-world evidence in sex differences in the clinical outcomes of NOACs comparing to different quality of warfarin treatment. This population-based cohort study was conducted to compare the effectiveness and safety outcomes of NOACs versus warfarin in men and women with stratifications for TTR, with the aim to provide insights into oral anticoagulant treatment choices with respect to the sex of the patients.

Methods

Data Source

The data used in this study was collected from the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS), which was developed by the Hospital Authority in Hong Kong. The Hospital Authority is a statutory body that manages public hospitals and outpatient clinics in the region, serving over 7 million people in Hong Kong (16). Clinical information is recorded by healthcare professionals and transferred to CDARS regularly (17,18). All medical records are anonymized with a unique reference number to protect patient confidentiality. Patient demographics and clinical records related to diagnosis, operation and procedure, drug use, accident and emergency visits, outpatient and inpatient visits, and laboratory tests were retrieved from CDARS for data analyses. CDARS has been used to conduct high-quality epidemiological studies in Hong Kong (17,18). International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes were used to identify the outcomes and comorbidities (Online Table 1). The reliability of the database was demonstrated by the high coding accuracy for the outcomes measured in this study, with a positive predictive value of 95% for AF, 90% for ischemic stroke, 95% for intracranial hemorrhage (ICH), and 100% for gastrointestinal bleeding (GIB) (17,18). The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference no. UW13-468).

Study Design

Cohort Selection

Patients with a new diagnosis of AF between 2010 and 2015 were identified from CDARS. Due to the lack of specific coding for non-valvular AF, patients with valvular heart diseases, valve replacement, or hyperthyroidism at or prior to their first AF occurrence were excluded in order to select patients with non-valvular AF only (19). Possible cases of transient or secondary AF were excluded if pericarditis, myocarditis, cardiac surgery, or

pulmonary embolism were recorded within 90 days before their first AF occurrence (19). Patients with missing sex or date of birth, under the age of 18, or who died at their first AF occurrence were also excluded.

The index date was defined as the start date of the first prescription of oral anticoagulants (warfarin, apixaban, dabigatran, or rivaroxaban) after the first AF diagnosis. Patients were assigned into the corresponding treatment groups with respect to the first identified oral anticoagulant prescription regardless of dosage. To select new patients, those who had oral anticoagulants within 180 days before the index date or more than one prescription of oral anticoagulants on the index date were excluded.

Outcomes

The primary outcome was defined as the composite of ischemic stroke/systemic embolism (SSE) for the measurement of effectiveness. Secondary outcomes including ICH, GIB, and all-cause mortality were the safety measures. The follow-up period started from the index date and was censored by the switch of anticoagulation treatment, discontinuation of treatment (i.e. a gap of greater than 5 days between two consecutive prescriptions), occurrence of outcomes, date of death, or study end date (i.e. December 31, 2016), whichever came first.

Statistical Analysis

Baseline patient characteristics were retrieved from CDARS for comparison between treatment groups in men and women. Continuous variables were expressed as mean±standard deviation while categorical data were reported as frequency (percentage).

Propensity score matching was used to control for the confounding due to non-randomized treatment decisions (20). Propensity scores were derived from logistic regression using covariates measured on and prior to the index date. The variables included age, index year, number of inpatient visits at one year before the index date, Charlson Comorbidity

Index, comorbidities prior to the index date, and current medication use (i.e. prescription records within 90 days prior to the index date). CHA_2DS_2-VASc and $CHADS_2$ score were calculated for the evaluation of the stroke risk, while modified HAS-BLED score was calculated for the estimation of the bleeding risk (21,22).

Propensity score matching was performed separately in men and women using the greedy variable-ratio matching algorithm (23). NOAC users (apixaban, dabigatran, and rivaroxaban) were matched to warfarin users at a 1:1 ratio with a caliper of 0.2 standard deviation of the propensity score. Two treatment groups were considered to be similar if the standardized difference of the covariates were less than 0.1 (negligible difference).

The risk of outcomes was compared between NOAC and warfarin groups in the specific sex using Cox proportional hazard regression stratified on propensity score matched pairs. Results were presented as hazard ratios (HR) with 95% confidence interval (CI). The *p* value for interaction was calculated as a post hoc analysis to statistically test for any differences in the outcomes with NOACs versus warfarin between men and women. A 2-sided *p* value of less than 0.05 was considered statistically significant.

Time in Therapeutic Range Analysis

TTR was calculated using the Rosendaal method which was developed with the assumption that international normalized ratio (INR) varies in proportion to time between two measurements (24). Due to the fluctuation of INR in the initial warfarin treatment, records measured within 28 days after the index date were excluded. Patients with less than 28 days of follow-up were excluded from the analysis to allow for a fair comparison. Inpatient INR records were also excluded to reduce the possibilities of patients having other forms of anticoagulation during hospitalization that may affect their INR. The Hospital Authority guideline for warfarin treatment specified that INR should be measured every eight weeks

(25). Therefore, INR records with a gap larger than 60 days were not interpolated for the accuracy of TTR calculation.

Propensity score matching was performed in men and women separately with the aforementioned method. We defined TTR≥60% as having a good INR control, while TTR<60% as having a poor INR control (18,26,27). Patients who did not have any INR measurement after the 28-day of drug initiation period, or did not have a regular INR measurement (i.e. all INR tests measured >60 days apart or not having regular outpatient INR tests) were categorized as "without routine INR monitoring". Matched patients were stratified into three subgroups for analysis according to the anticoagulation control: 1) good INR control, 2) poor INR control, and 3) without routine INR monitoring.

Statistical analyses were conducted independently by two coauthors (S.W.Y.L. and W.C.Y.L.) using RStudio 1.0.143 (RStudio Inc., MA, United States) and Statistical Analysis System v9.3 (SAS Inc., NC, United States). Results were independently cross-checked for quality assurance.

Results

Baseline Characteristics and Treatment Choices

There were 61,893 patients with a new diagnosis of AF between 2010 and 2015 in CDARS (**Figure 1**). Following the exclusion criteria, 15,292 patients were included in the analyses, with 48% being women. Among the study cohort, 45% of men and 50% of women were prescribed NOACs after the first diagnosis of AF (Online Table 2). After propensity score matching, 4,972 men and 4,834 women were successfully matched at a 1:1 ratio respectively (**Figure 1**). Both men and women have similar baseline characteristics between the two treatment groups, where all standardized differences were less than 0.1 (**Table 1**).

Among the matched NOAC users, dabigatran (63% of men and 63% of women) was the most commonly used drug, followed by rivaroxaban (28% of men and 27% of women)

and apixaban (9% of men and 10% of women). There were 41% of men and 32% of women receiving standard doses (Online Table 3).

The mean age of the matched cohort was 71.7±10.8 years for men and 75.8±10.1 years for women. Both the mean CHA_2DS_2-VASc score and HAS-BLED score were higher in women (4.34±1.79 and 2.74±1.24 respectively) than in men (2.96±1.68 and 2.59±1.27 respectively). The mean follow-up time was 1.23±1.33 years in men and 1.29±1.40 years in women.

Main Analysis

Primary Outcome

Results of the main analysis before propensity score matching are presented in **Online Table 4**. After propensity score matching, 152 (6.11%) warfarin users and 140 (5.63%) NOAC users experienced SSE in the men cohort, while 191 (7.90%) warfarin users and 153 (6.33%) NOAC users had SSE in the women cohort. Results from the Cox regression analysis did not show a significant difference in the risk of SSE for NOACs versus warfarin in both sexes (**Table 2**). There was a trend for a lower risk of SSE in women with marginally non-significant values (HR: 0.81; 95% CI: 0.63 to 1.03).

Secondary Outcomes

NOAC use was associated with a significantly lower risk of ICH (HR: 0.16; 95% CI: 0.06 to 0.40) and all-cause mortality (HR: 0.55; 95% CI: 0.39 to 0.77) when compared to warfarin in women (**Table 2**). Conversely, there were no significant differences between the treatment groups in all safety outcomes among the men cohort. The *p* value for interaction was statistically significant for ICH only.

Time in Therapeutic Range Analysis

After excluding 1,540 men and 1,434 women with less than 28 days of follow-up, 3,972 men and 3,782 women were successfully matched by propensity scores respectively

(**Figure 2 and 3**). Among the matched warfarin users, 78.6% of men and 78.9% of women had valid INR records for the calculation of TTR during the follow-up period. The mean TTR was 45.1±29.1% for men and 46.0±29.0% for women. The median INR for men and women were 2.10 (interquartile range=0.84) and 2.10 (interquartile range=0.80) respectively.

Results of the TTR analysis before propensity score matching are presented in **Online Table 5**. After propensity score matching, a significant risk reduction in SSE amongst NOAC users when compared to warfarin users without routine INR monitoring was observed in both men (HR: 0.21; 95% CI: 0.08 to 0.55) and women (HR: 0.24; 95% CI: 0.09 to 0.63) (**Table 3**). There was not a significant difference in the risk of SSE in NOAC and warfarin users with routine INR monitoring in both sexes, irrespective of the quality of INR control (good or poor).

Analyzing safety outcomes, NOAC use was associated with a significantly lower risk of GIB and all-cause mortality when compared to warfarin users without routine INR monitoring in both men (GIB=[HR: 0.08; 95% CI: 0.01 to 0.64]; all-cause mortality=[HR: 0.11; 95% CI: 0.03 to 0.35]) and women (GIB=[HR: 0.20; 95% CI: 0.06 to 0.69]; all-cause mortality=[HR: 0.10; 95% CI: 0.03 to 0.27]). Between the two sexes, only women on NOACs had a lower risk of ICH when compared to warfarin users with routine INR monitoring (good INR control=[HR: 0.13; 95% CI: 0.02 to 1.00] and poor INR control=[HR: 0.20; 95% CI: 0.04 to 0.91]).

Discussion

This study demonstrates sex-specific clinical outcomes for NOACs versus warfarin. Although the risk of SSE with NOACs (versus warfarin) was comparable among men and women, NOAC use was associated with a lower risk of ICH and all-cause mortality in women but not in men. On stratifications of TTR, NOAC use was associated with a risk reduction in SSE, GIB, and all-cause mortality when compared to warfarin users without

routine INR monitoring in both sexes. The association of a lower risk of ICH in the women cohort remained when comparing NOAC users to warfarin users with routine INR monitoring, regardless of the quality of the anticoagulation control. The significant *p* value for interaction in the main analysis demonstrates the potential sex difference in ICH outcome.

Women have in general been underrepresented in cardiovascular clinical trials. In the previous major trials of warfarin, only 25% of the participants were women (28,29). Despite the increase in the proportion of women to around 40% in the more recent NOAC trials, these trials were not designed to study sex-specific outcomes (29). The lack of trial evidence data makes it difficult to optimize oral anticoagulation therapy with respect to the sex of patients in real-world practice. Sex-specific analysis is particularly important as women appear to have different utilization patterns and metabolism of anticoagulants when compared with men (6,10,30). This highlights the importance of assessing the effectiveness and safety of NOACs versus warfarin in the sexes.

There are limited evidence in the literature investigating sex differences in the treatment outcomes of oral anticoagulants. One meta-analysis pooled the results from four landmark randomized controlled trials (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials) and found a significant lower risk of stroke/systemic embolism for NOACs versus warfarin in both men and women, and the *p* value for interaction was not statistically significant (31). However, the benefit of NOACs in stroke/systemic embolism in the meta-analysis was mainly driven by hemorrhagic stroke, which was not included in the SSE outcome in our study. Regarding the safety outcomes, although the *p* value for interaction was not significant in the major bleeding outcome in the meta-analysis, the significant lower risk of major bleeding was only found in women for NOACs versus warfarin. Of note, major bleeding was a composite of multiple types of bleeding outcomes, which was not directly comparable to the ICH and GIB outcomes in our study.

Two other meta-analyses compared the risk of outcomes for men versus women in the specific treatment groups. Pancholy et al. did not find any differences in stroke/systemic embolism between men and women on NOACs but there was a lower risk of major bleeding in women when compared to men. Conversely, women on warfarin had a significantly greater risk of stroke/systemic embolism but a similar risk of major bleeding. Therefore, it is concluded that there was a net clinical benefit of NOACs compared to warfarin in women with AF (13). Proietti et al. pooled the results from the NOAC groups of different trials and found that men were more protected from stroke/systemic embolism and women were more protected from major bleeding (32). With the different study designs, selection of cohort, and definition of outcomes, it is difficult to compare our results with the results of the RCTs and meta-analyses. However, it is important to note that all major trials of NOACs were not designed or statistically powered to conduct sex-specific analyses (28). Studies in the real-world population outside the restrictive trial setting are warranted to investigate the actual outcomes of oral anticoagulants in clinical practice.

Two observational studies have described sex differences in the clinical outcomes for NOACs versus warfarin (33,34). However, these studies did not consider the quality of the anticoagulation control or address the class effects of NOACs versus warfarin. In the study using the administrative data in Canada, women on high-dose dabigatran (150 mg twice daily) had a trend towards a lower risk of stroke but a similar risk of bleeding when compared to warfarin users, while men experienced a similar risk of stroke but a lower risk of bleeding (33). Another cohort study using American data demonstrated a similar risk of stroke and a higher risk of bleeding in women for rivaroxaban versus warfarin, while a lower risk of stroke and similar risk of bleeding was observed in men (34). Analyses for bleeding subtypes showed that dabigatran use was associated with a lower risk of ICH in both sexes in their cohort (34). However, our study using Asian clinical data showed that NOAC use was

associated with a lower risk of ICH and all-cause mortality when compared to warfarin users in women only. Although the result was not statistically significant, women on NOACs had a trend for being more protected from SSE when compared with warfarin.

To date, the precise reasons for the different effects of NOACs versus warfarin among men and women remain unknown. It has been proposed that the fluctuation of anticoagulation effects from warfarin may contribute to the sex differences in clinical outcomes of warfarin users (13). In general, women have a lower mean body mass or hepatic fat content (29). This may predispose to the sex differences in the metabolism of warfarin by cytochrome P450 enzymes, leading to a different pharmacological response and outcomes of warfarin among men and women (29). Further prospective studies are required to evaluate the sex differences in the clinical outcomes of NOACs versus warfarin based on the different mechanism of action of the drugs. Indeed, women seem to have a poorer anticoagulation control. Female sex is a component of the SAMe-TT_2R_2 score, a prediction model of poor INR control (35). It is thus important to account for the quality of warfarin treatment in the risk comparison with NOACs.

In the TTR analysis, our results showed that NOACs were more effective in reducing the risk of SSE, GIB, and all-cause mortality when compared to patients on warfarin without routine INR monitoring in both men and women. This finding highlights the importance of regular INR measurements for warfarin patients and is in line with the suggestion that regular INR monitoring plays a major role in achieving better clinical outcomes among warfarin users (36).

Among patients on warfarin with routine INR monitoring, statistical significant differences were observed in ICH for NOACs versus warfarin with both good and poor INR control in women only. This finding further strengthens the potential better clinical outcomes of NOACs in women, even after consideration of TTR. However, the risk of stroke was

comparable between the two treatment groups in both sexes. Indeed, TTR was calculated based on the INR target range of 2.0-3.0 as recommended in the guidelines (4,5). With regards to the sex and ethnic differences, a different INR target range may be required for Asians, especially for Asian women. Previous studies have demonstrated that the Asian population may benefit more from a lower INR target if they were prescribed warfarin (37,38); however, these studies have not assessed the quality of anticoagulation control with the use TTR.

Ethnic differences in stroke and bleeding risk have been suggested, with Asians having a higher risk of stroke and being more prone to bleeding when prescribed warfarin (39). The metabolism of warfarin may be different due to the genetic polymorphism of cytochrome P450 enzymes and vitamin K epoxide reductase complex subunit 1 across different ethnic groups (39). However, clinical trials have only involved a small number of Asian participants and women (29,40). The restrictive environment of the trials may not reflect the complex clinical scenarios in the day-to-day clinical settings, particularly in Asia where clinical practice may be considered to be more conservative (41). This is partly reflected in our cohort where patients on warfarin had a low TTR and a high percentage of NOAC users received the reduced doses. Nevertheless, the use of Hong Kong Chinese clinical data demonstrated the dosing patterns in the real-life clinical practice, which may not necessarily be the manufacturer recommended dosing patterns.

Strengths and Limitations

To our knowledge, this is the first observational study using the real-world data to present sex differences with consideration of anticoagulation control in warfarin users. The use of propensity score matching, clinical data representing predominantly Asian ethnicity, and comparison of sex-specific outcomes between drug classes adds strength to our study.

The availability of INR test results, drug dispensing history, and diagnosis records allowed for reliable calculations of TTR, where similar data was not available in prior studies.

Nonetheless, several limitations of our study should be noted. First, similar to other epidemiological studies, there may be residual confounding as inherent in the observational study design. To overcome this potential limitation, all important confounding factors for which there was adequate information available were included and addressed in this study. Propensity score matching was used and the baseline characteristics were well balanced between the treatment groups in both sexes. Second, NOACs were combined as a group for comparison with warfarin. There could be potential differences in the outcomes between each NOAC, however, there is limited evidence from the current literature to demonstrate the magnitude of the potential differences. This study was conducted based on the pharmacological basis that women may not respond as well when they are prescribed warfarin, a vitamin K antagonist. The approach of combining all NOACs as a single group increased the sample size to achieve adequate statistical power. Third, although the quality of anticoagulation control in the warfarin group was assessed with the use of TTR, the actual adherence in the NOAC group could not be assessed with the use of dispensing records. In particular, similar to other epidemiological studies, the discontinuation of medications was censored using the gap between each dispensing record but not by the actual intake of the medications, which is not available. However, as the mean duration of NOAC use in our cohort was more than one year; it is unlikely that patients continued to collect prescriptions for a drug that they have not been using for such a long period. Finally, our post hoc analysis may not have sufficient power to demonstrate the significant *p* value for interaction for all-cause mortality in the main analysis and ICH in the TTR analysis, although the significant lower risk of these outcomes were only found in women. Of note, our per-protocol analysis was to compare the clinical outcomes of NOACs versus warfarin within men and within

women, respectively. We aimed to provide sex-specific data to inform oral anticoagulant prescribing with respect to the sex of patients in clinical practice.

Conclusions

In men, comparable clinical outcomes were observed with NOACs versus warfarin. In women, NOAC use was associated with a lower risk of ICH and all-cause mortality when compared with warfarin. Routine INR monitoring may result in comparable clinical outcomes between NOACs and warfarin in both sexes. However, a lower risk of ICH remained in women on NOACs when they were compared to warfarin users with both good and poor INR control.

Perspectives

Competency in Medical Knowledge: This study provided further evidence to guide the choice of oral anticoagulants as thromboprophylaxis in patients with AF with respect to the specific sex. Considering the lower risk of ICH and all-cause mortality with a similar risk of stroke and GIB, women may benefit more from NOACs than from warfarin. However, this is not observed in men.

Translational Outlook: Further prospective studies should evaluate the sex differences in the clinical outcomes of NOACs versus warfarin based on the quality of the anticoagulation control.

References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837-47.
2. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol 2014;11:639-54.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:2071-104.
5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609-78.
6. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012;307:1952-8.
7. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM 2014;107:955-67.
8. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol 2016;13:321-32.
9. Gillis AM. Atrial Fibrillation and Ventricular Arrhythmias: Sex Differences in Electrophysiology, Epidemiology, Clinical Presentation, and Clinical Outcomes. Circulation 2017;135:593-608.

10. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost 2014;111:385-91.

11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.

12. Humphries KH, Kerr CR, Connolly SJ, et al. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 2001;103:2365-70.

13. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol 2014;113:485-90.

14. Senoo K, Lip GY. Female Sex, Time in Therapeutic Range, and Clinical Outcomes in Atrial Fibrillation Patients Taking Warfarin. Stroke 2016;47:1665-8.

15. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). Am J Cardiol 2012;110:1799-802.

16. Hospital Authority. Introduction. Available at: http://www.ha.org.hk. Accessed August 7, 2017.

17. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology 2015;149:586-95.

18. Chan EW, Lau WC, Siu CW, et al. Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with

nonvalvular atrial fibrillation: A population-wide cohort study. Heart Rhythm 2016;13:1581-8.

19. Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. Circ Cardiovasc Qual Outcomes 2013;6:567-74.

20. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014;275:570-80.

21. Chen PC, Lip GY, Yeh G, Lin HJ, Chien KL. Risk of bleeding and stroke with oral anticoagulation and antiplatelet therapy in patients with atrial fibrillation in Taiwan: a nationwide cohort study. PloS One 2015;10:e0125257.

22. Fischer GE, Bialek SP, Homan CE, Livingston SE, McMahon BJ. Chronic liver disease among Alaska-Native people, 2003-2004. Am J Gastroenterol 2009;104:363-70.

23. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. Pharmacoepidemiol Drug Saf 2012;21(Suppl 2):S69-S80.

24. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.

25. Chan PH, Hai JJ, Chan EW, et al. Use of the SAMe-TT2R2 Score to Predict Good Anticoagulation Control with Warfarin in Chinese Patients with Atrial Fibrillation: Relationship to Ischemic Stroke Incidence. PloS One 2016;11:e0150674.

26. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international

normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029-37.

27. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167:239-45.

28. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes 2010;3:135-42.

29. Ko D, Rahman F, Martins MA, et al. Atrial fibrillation in women: treatment. Nat Rev Cardiol 2017;14:113-24.

30. Lane S, Al-Zubiedi S, Hatch E, et al. The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors. Br J Clin Pharmacol 2012;73:66-76.

31. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.

32. Proietti M, Cheli P, Basili S, Mazurek M, Lip GY. Balancing thromboembolic and bleeding risk with non-vitamin K antagonist oral anticoagulants (NOACs): A systematic review and meta-analysis on gender differences. Pharmacol Res 2017;117:274-82.

33. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Pilote L. Sex Differences in Dabigatran Use, Safety, And Effectiveness In a Population-Based Cohort of Patients With Atrial Fibrillation. Circ Cardiovasc Qual Outcomes 2015;8:593-9.

34. Palamaner Subash Shantha G, Bhave PD, Girotra S, et al. Sex-Specific Comparative Effectiveness of Oral Anticoagulants in Elderly Patients With Newly Diagnosed Atrial Fibrillation. Circ Cardiovasc Qual Outcomes 2017;10:e003418.

35. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. Chest 2013;144:1555-63.

36. Witt DM, Delate T, Clark NP, et al. Nonadherence with INR monitoring and anticoagulant complications. Thromb Res 2013;132:e124-30.

37. You JH, Chan FW, Wong RS, Cheng G. Is INR between 2.0 and 3.0 the optimal level for Chinese patients on warfarin therapy for moderate-intensity anticoagulation? Br J Clin Pharmacol 2005;59:582-7.

38. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. Intern Med 2001;40:1183-8.

39. Chiang CE, Wang KL, Lip GYH. Stroke prevention in atrial fibrillation: An Asian perspective. Thromb Haemost 2014;111:789-97.

40. Chiang CE, Wang KL, Lin SJ. Asian strategy for stroke prevention in atrial fibrillation. Europace 2015;17 Suppl 2:ii31-9.

41. Chan YH, Kuo CT, Yeh YH, et al. Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation. J Am Coll Cardiol 2016;68:1389-401.

Figure Titles and Legends

Central Illustration. Kaplan-Meier Curves for Intracranial Hemorrhage and All-cause Mortality in Men and Women. NOAC=non-vitamin K antagonist oral anticoagulant.

Figure 1. Cohort Selection for the Main Analysis. CDARS=Clinical Data Analysis and Reporting System; NOAC=non-vitamin K antagonist oral anticoagulant.

Figure 2. Cohort Selection for Men in the Time in Therapeutic Range Analysis. INR=international normalized ratio; NOAC=non-vitamin K antagonist oral anticoagulant; TTR=time in therapeutic range.

Figure 3. Cohort Selection for Women in the Time in Therapeutic Range Analysis. NOAC=non-vitamin K antagonist oral anticoagulant; INR=international normalized ratio; TTR=time in therapeutic range.

Table 1. Baseline Characteristics after Propensity Score Matching

	Men			Women		
	Warfarin	**NOAC**	**Standardized difference**	**Warfarin**	**NOAC**	**Standardized difference**
No. of patients	2486	2486		2417	2417	
Age (mean ± SD)	71.83±10.79	71.58±10.86	0.023	75.87±10.55	75.78±9.63	0.010
CHA_2DS_2-VASc (mean ± SD)	2.96±1.68	2.96±1.68	0.005	4.34±1.82	4.34±1.75	<0.001
$CHADS_2$ (mean ± SD)	1.98±1.40	1.99±1.39	0.001	2.29±1.53	2.27±1.49	0.016
HAS-BLED (mean ± SD)	2.58±1.27	2.59±1.26	0.009	2.73±1.27	2.74±1.21	0.009
No. of inpatient visit (mean ± SD)	1.82±1.79	1.84±1.81	0.014	1.90±1.80	1.89±1.94	0.002
CCI (mean ± SD)	1.48±1.50	1.46±1.48	0.016	1.42±1.46	1.41±1.41	0.003
Comorbidities (%)						
Congestive heart failure	612 (24.6)	603 (24.3)	0.008	641 (26.5)	636 (26.3)	0.005
Hypertension	1,196 (48.1)	1,221 (49.1)	0.020	1,371 (56.7)	1,343 (55.6)	0.023
Stroke	733 (29.5)	737 (29.6)	0.004	741 (30.7)	738 (30.5)	0.003
Vascular disease	601 (24.2)	589 (23.7)	0.011	498 (20.6)	488 (20.2)	0.010
Diabetes	563 (22.6)	562 (22.6)	0.001	568 (23.5)	573 (23.7)	0.005
Intracranial hemorrhage	81 (3.3)	80 (3.2)	0.002	67 (2.8)	63 (2.6)	0.010
Gastrointestinal bleeding	194 (7.8)	192 (7.7)	0.003	173 (7.2)	165 (6.8)	0.013

Other bleeding	230 (9.3)	234 (9.4)	0.006	174 (7.2)	181 (7.5)	0.011
Renal disease	210 (8.4)	203 (8.2)	0.010	171 (7.1)	163 (6.7)	0.013
Medication use within 90 days before the index date (%)						
Antiplatelet	1,791 (72.0)	1,800 (72.4)	0.008	1,769 (73.2)	1,774 (73.4)	0.005
ACEI/ARB	1,214 (48.8)	1,203 (48.4)	0.009	1,141 (47.2)	1,161 (48.0)	0.017
Beta blocker	1,421 (57.2)	1,414 (56.9)	0.006	1,508 (62.4)	1,488 (61.6)	0.017
Calcium channel blocker	1,304 (52.5)	1298 (52.2)	0.005	1,444 (59.7)	1,439 (59.5)	0.004
Amiodarone	251 (10.1)	260 (10.5)	0.012	333 (13.8)	311 (12.9)	0.027
Dronedarone	18 (0.7)	19 (0.8)	0.005	18 (0.7)	16 (0.7)	0.010
Statin	1,264 (50.8)	1,260 (50.7)	0.003	1,177 (48.7)	1,180 (48.8)	0.002
NSAID	148 (6.0)	161 (6.5)	0.022	138 (5.7)	142 (5.9)	0.007
H_2 antagonist	1,295 (52.1)	1,320 (53.1)	0.020	1,366 (56.5)	1,389 (57.5)	0.019
Proton pump inhibitor	663 (26.7)	671 (27.0)	0.007	670 (27.7)	654 (27.1)	0.015
SSRI	31 (1.2)	27 (1.1)	0.015	89 (3.7)	93 (3.8)	0.009
HRT	NA	NA	NA	5 (0.2)	4 (0.2)	0.010

ACEI/ARB=angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCI=Charlson comorbidity index; $CHADS_2$=Congestive heart failure, Hypertension, Age≥75 years, Diabetes, Stroke; CHA_2DS_2-VASc=Congestive heart failure, Hypertension, Age≥75 years (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age (65-74 years), and Sex (female); NOAC=non-vitamin K antagonist oral anticoagulant; HAS-BLED=Hypertension, Abnormal liver or kidney function, Stroke history, Bleeding history, Labile INR (not included), Elderly (Age>65 years), Drug, and alcohol use; HRT=hormone replacement therapy; NSAID=non-steroidal anti-inflammatory drug; SD=standard deviation; SSRI=selective serotonin receptor inhibitor.

Table 2. Risk of Clinical Outcomes in Men and Women after Propensity Score Matching

	Men (n=4,972)			**Women (n=4,834)**			***P* value for interaction**
	No. of event / follow-up time* / incidence†	**HR (95% CI)**	***P* value**	**No. of event / follow-up time* / incidence†**	**HR (95% CI)**	***P* value**	
Ischemic stroke/systemic embolism							
Warfarin	152 / 2,942 / 5.17	Reference		191 / 3,007 / 6.35	Reference		-
NOAC	140 / 3,188 / 4.39	0.85 (0.65-1.12)	0.247	153 / 3,252 / 4.71	0.81 (0.63-1.03)	0.089	0.758
Intracranial hemorrhage							
Warfarin	38 / 3,123 / 1.22	Reference		54 / 3,205 / 1.68	Reference		-
NOAC	26 / 3,336 / 0.78	0.55 (0.27-1.10)	0.091	15 / 3,426 / 0.44	0.16 (0.06-0.40)	<0.001	0.037
Gastrointestinal bleeding							
Warfarin	73 / 3,069 / 2.38	Reference		97 / 3,135 / 3.09	Reference		-
NOAC	86 / 3,288 / 2.62	1.13 (0.73-1.74)	0.583	94 / 3,359 / 2.80	0.89 (0.63-1.27)	0.528	0.410
All-cause mortality							
Warfarin	137 / 3,128 / 4.38	Reference		157 / 3,218 / 4.88	Reference		-
NOAC	121 / 3,348 / 3.61	0.83 (0.59-1.16)	0.271	98 / 3,431 / 2.86	0.55 (0.39-0.77)	<0.001	0.087

*Follow-up time is presented as total number of person-years. †Incidence is presented as no. of events per 100 person-years.

CI=confidence interval; HR=hazard ratio.

Table 3. Risk of Clinical Outcomes Stratified by Time in Therapeutic Range in Men and Women after Propensity Score Matching

		Men (n=3,972)			**Women (n=3,782)**			***P* value for interaction**
		No. of event / follow-up time* / incidence†	**HR (95% CI)**	***P* value**	**No. of event / follow-up time* / incidence†**	**HR (95% CI)**	***P* value**	
Good INR control (TTR ≥ 60%)								
SSE	Warfarin	16 / 1,085 / 1.47	Reference		23 / 1,208 / 1.90	Reference		-
	NOAC	14 / 786 / 1.78	1.57 (0.61-4.05)	0.350	14 / 824 / 1.70	1.44 (0.62-3.38)	0.396	0.897
ICH	Warfarin	12 / 1,094 / 1.10	Reference		15 / 1,226 / 1.22	Reference		-
	NOAC	2 / 804 / 0.25	0.29 (0.06-1.38)	0.118	1 / 835 / 0.12	0.13 (0.02-1.00)	0.050	0.534
GIB	Warfarin	19 / 1,081 / 1.76	Reference		30 / 1,201 / 2.50	Reference		-
	NOAC	19 / 787 / 2.41	1.57 (0.61-4.05)	0.350	20 / 823 / 2.43	1.23 (0.59-2.56)	0.578	0.689
All-cause mortality	Warfarin	26 / 1,095 / 2.37	Reference		31 / 1,231 / 2.52	Reference		-
	NOAC	18 / 804 / 2.24	1.40 (0.62-3.15)	0.416	17 / 837 / 2.03	1.00 (0.48-2.10)	1.000	0.549
Poor INR control (TTR < 60%)								
SSE	Warfarin	35 / 1,814 / 1.93	Reference		37 / 1,773 / 2.09	Reference		-
	NOAC	33 / 1,594 / 2.07	1.13 (0.65-1.98)	0.668	32 / 1,528 / 2.09	1.77 (0.90-3.49)	0.100	0.319
ICH	Warfarin	16 / 1,867 / 0.86	Reference		18 / 1,785 / 1.01	Reference		-
	NOAC	13 / 1,628 / 0.80	0.88 (0.32-2.41)	0.796	4 / 1,560 / 0.26	0.20 (0.04-0.91)	0.038	0.113
GIB	Warfarin	37 / 1,838 / 2.01	Reference		36 / 1,790 / 2.04	Reference		-
	NOAC	30 / 1,615 / 1.86	1.12 (0.57-2.21)	0.732	32 / 1,561 / 2.10	0.95 (0.52-1.76)	0.876	0.720

All-cause mortality	Warfarin	65 / 1,869 / 3.48	Reference		49 / 1,790 / 2.74	Reference		-
	NOAC	61 / 1,636 / 3.73	1.15 (0.72-1.82)	0.559	38 / 1,561 / 2.43	1.14 (0.64-2.05)	0.655	0.992
Without routine INR monitoring								
SSE	Warfarin	25 / 167 / 14.97	Reference		25 / 145 / 17.22	Reference		-
	NOAC	18 / 633 / 2.84	0.21 (0.08-0.55)	0.001	19 / 597 / 3.18	0.24 (0.09-0.63)	0.004	0.849
ICH	Warfarin	7 / 207 / 3.38	Reference		16 / 170 / 9.42	Reference		-
	NOAC	2 / 652 / 0.31	NA‡	NA‡	4 / 612 / 0.65	NA‡	NA‡	NA‡
GIB	Warfarin	15 / 195 / 7.70	Reference		17 / 159 / 10.71	Reference		-
	NOAC	9 / 645 / 1.39	0.08 (0.01-0.64)	0.017	19 / 596 / 3.19	0.20 (0.06-0.69)	0.011	0.472
All-cause mortality	Warfarin	34 / 208 / 16.35	Reference		47 / 174 / 27.01	Reference		-
	NOAC	20 / 652 / 3.07	0.11 (0.03-0.35)	<0.001	20 / 613 / 3.26	0.10 (0.03-0.27)	<0.001	0.883

*Follow-up time is presented as total number of person-years. †Incidence is presented as no. of events per 100 person-years. ‡Results not available due to low number of events.

CI=confidence interval; GIB=Gastrointestinal bleeding; HR=hazard ratio; ICH=Intracranial hemorrhage; INR=international normalized ratio; SSE=Ischemic stroke/systemic embolism; TTR=time in therapeutic range.