



# BMJ Open Influence of gender on the clinical outcomes of Asian non-valvular atrial fibrillation patients: insights from the prospective multicentre COOL-AF registry

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## ABSTRACT

**Objective** To determine the effect of gender on clinical outcomes of Asian non-valvular atrial fibrillation patients.

**Design** This is a cohort study.

**Setting** 27 university and regional hospitals in Thailand.

**Participants** Patients with non-valvular atrial fibrillation.

**Primary and secondary outcomes measures** The clinical outcomes were ischaemic stroke/transient ischaemic attack (TIA), major bleeding, intracerebral haemorrhage (ICH), heart failure and death. Follow-up data were recorded every 6 months until 3 years. Differences in clinical outcomes between males and females were determined. Multivariate analysis was performed to assess the effect of gender on clinical outcomes. Survival analysis and log-rank test were performed to determine the time-dependent effect of clinical outcomes, and the difference between males and females. Effect of oral anticoagulant (OAC) on outcomes and net clinical benefit of OAC was assessed. The analysis was performed both for the whole dataset and propensity score matching with multiple imputation.

**Results** A total of 3402 patients (mean age: 67.4±11.3 years; 58.2% male) were included. Average follow-up duration 25.7±10.6 months (7192.6 persons-year). Rate of ischaemic stroke/TIA, major bleeding, ICH, heart failure and death were 1.43 (1.17–1.74), 2.11 (1.79–2.48), 0.70 (0.52–0.92), 3.03 (2.64–3.46) and 3.77 (3.33–4.25) per 100 person-years. Females had increased risk for ischaemic stroke/TIA and heart failure and males had increased risk for major bleeding and ICH. Ischaemic stroke/TIA risk in females and major bleeding and ICH risk in males remained even after correction for age, comorbid conditions and anticoagulation treatment. OAC reduced the risk of ischaemic stroke/TIA in males and females, and markedly increased the risk of major bleeding and ICH in males.

**Conclusions** Females had a higher risk of ischaemic stroke/TIA and heart failure, and a lower risk of major bleeding and ICH compared with males. OAC reduced risk of ischaemic stroke/TIA in females, and markedly increased risk of major bleeding and ICH in males.

## Strengths and limitations of this study

- This is a prospective nationwide multicentre non-valvular atrial fibrillation registry.
- Site monitoring was performed to ensure the quality of data collection and management at every study site.
- The adjudication committee validated all clinical outcomes.
- The 27 hospitals that contribute data to the COhort of antithrombotic use and Optimal INR Level in patients with non-valvular atrial fibrillation registry are all large hospitals. Therefore, our findings may not generalisable to lower-level care settings.
- Due to the low proportion of non-vitamin K antagonist oral anticoagulant (NOAC) use, the results of this study may not be comparable to those reported from countries with a high rate of NOAC prescription.

## INTRODUCTION

Non-valvular atrial fibrillation (NVAf) is one of the major causes of ischaemic stroke with an increased risk of approximately five times compared with those without NVAf.<sup>1</sup> Published guidelines recommend that patients with high or intermediate risk for ischaemic stroke be given oral anticoagulants (OAC), and non-vitamin K antagonist OACs (NOAC) are preferred over warfarin.<sup>2–4</sup> Female gender is one of the components in the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system (C = congestive heart failure; H = hypertension; A = age>75 years; D = diabetes; S = stroke; V = vascular disease; A = age 65–74; and Sc = female sex category).<sup>5</sup> Previous studies reported that female gender increased the risk of ischaemic stroke compared with male gender.<sup>6 7</sup> The increased risk in female patients is mainly among the elderly subset. Therefore, in

females aged less than 65 years, it is recommended that no score be given to the female gender component.<sup>2</sup>

A 2017 study suggested that the increased risk of ischaemic stroke in Asian NVAF women is similar to that of their Western female counterparts.<sup>8</sup> However, previous reports from Taiwan and Japan indicated that female gender may not be a risk factor for stroke.<sup>9 10</sup> Recent recommendations suggested that a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 or more, and of 2 or more should define high risk for ischaemic stroke in females and males, respectively.<sup>2 4</sup> Some experts suggested that female gender should be a risk modifier rather than a risk factor, and they proposed the use of a non-gender CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system to simplify the way stroke risk is calculated.<sup>11</sup>

In this study, we aimed to investigate the influence of gender on the risk of ischaemic stroke, major bleeding, intracerebral haemorrhage (ICH), heart failure and death among Asian patients with NVAF using recent data from a nationwide multicentre registry in Thailand.

## METHODS

### Study population

The data including in this study are from the COhort of antithrombotic use and Optimal INR Level in patients with non-valvular atrial fibrillation in Thailand (COOL-AF) which is a prospective registry, which was established to collect NVAF patient data from 27 large hospitals in Thailand during 2014–2017. Patients with NVAF and age more than 18 years were enrolled. Patients with any of the following criteria were excluded: prosthetic heart valve, rheumatic mitral valve disease, recent ischaemic stroke within 3 months, NVAF from transient reversible cause (such as during pneumonia), life expectancy less than 3 years, pregnancy, thrombocytopenia (<100 000/mm<sup>3</sup>), myeloproliferative diseases, refusal to be enrolled and/or could not come for follow-up.<sup>12</sup> Each patient gave written informed consent before participation.

### Patient and public involvement

Patient and public was not involved in the study design or in the conduct of the study.

### Study protocol

After the informed consent process, site investigators reviewed medical records and interviewed patients to obtain data germane to this study. Investigators recorded the required data in the case record form established for this study. To reduce the bias, all investigators were instructed to enrol consecutive cases. All data were then uploaded into a web-based system. A research assistant at the data management centre rechecked and validated the data, and then double-entered the data to ensure the completeness and correctness of all study data. Flagged errors, omissions or other questions relating to study data were brought to the attention of site investigators for immediate clarification and resolution. Follow-up data from each 6-month follow-up visit until the 3-year time

point were entered into a case record form and managed similar to baseline data. Site monitoring was performed at every participating site to ensure that all data are correct and of good quality.

### Data collection

The following data were collected at baseline: demographic data, weight, height, vital signs, physical examination data, medical history (including comorbid conditions), each component of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and HAS-BLED score (H = uncontrolled hypertension, A = abnormal renal, or liverfunction; S = history of stroke; B = history of bleeding; L = labile INR; E = elderly (age above 65 years); and, D = Drugs or alcohol) laboratory data and medications, including antithrombotic drugs. Date of each clinical outcome was also recorded.

### Outcomes

The main outcomes were ischaemic stroke/transient ischaemic attack (TIA), major bleeding, ICH, heart failure and death. In addition to reporting the occurrence of a primary outcome, investigators were required to upload all supporting documentation for later review by the adjudication committee. Similar to routine data collection, site investigators were contacted for additional data, details and/or clarification if any questions about a primary outcome arose. The sample size of this registry was enough to determine the differences in outcome between two genders.

Ischaemic stroke was defined as a sudden onset of neurological deficit that lasted at least 24 hours and that was caused by a disruption of blood flow to the brain. TIA was a neurological deficit that lasted less than 24 hours. Major bleeding was defined by the criteria of the International Society of Thrombosis and Haemostasis,<sup>13</sup> which includes fatal bleeding, bleeding in a critical area or organ, bleeding that results in a decrease in haemoglobin level of 20 g/L or more, and/or bleeding that requires a transfusion of two units of red cells or more.

### Statistical analysis

Data were described as mean and SD for continuous data, and as number and percentage for categorical data. Comparisons of continuous data were made by Student's t-test for unpaired data. Categorical data were compared by  $\chi^2$  test or Fisher's exact test. Poisson model was used to estimate rate of clinical outcome as person-years with the number of events as the dependent variable and the log of person-time as an offset. Only the first occurrence of each event was counted. Univariate and multivariate analysis was performed to assess the effect of gender on clinical outcomes, and those results are shown as unadjusted and adjusted HR and 95% CI. HRs and 95% CIs for clinical outcomes were adjusted for the following potential confounders: age, type of atrial fibrillation, history of heart failure, history of coronary artery disease (CAD), diabetes mellitus, hypertension, dyslipidaemia, smoking, renal replacement therapy, history of bleeding,

anticoagulant use and antiplatelet use. Propensity score matching 1:1 for male and female with multiple imputation was performed to assess the effect of gender on clinical outcomes. The following factors were used to match male and female groups during propensity score matching: age, type of atrial fibrillation, history of heart failure, history of CAD, diabetes mellitus, hypertension, dyslipidaemia, smoking, renal replacement therapy, history of bleeding, anticoagulant use and antiplatelet use. Kaplan-Meier plot was used to display the cumulative event rate over time. The survival analysis was performed with the adjustment of the same factors adjusted during multivariate analysis. The net clinical benefit (NCB) of OAC versus no OAC was calculated using the following formula for both genders:  $(\text{ischaemic stroke/TIA rate}_{\text{off OAC}} - \text{ischaemic stroke/TIA rate}_{\text{on OAC}}) - 1.5 (\text{ICH rate}_{\text{on OAC}} - \text{ICH rate}_{\text{off OAC}})$ .<sup>14</sup> The NCB of NOAC vs warfarin was also calculated. A  $p < 0.05$  was considered statistically significant.

## RESULTS

### Study population

We enrolled a total of 3402 patients from 27 hospitals. Mean age was  $67.4 \pm 11.3$  years, and 1980 (58.2%) patients were male. Baseline characteristics of male and female patients are shown in [table 1](#). The mean  $\text{CHA}_2\text{DS}_2\text{-VASc}$  and HAS-BLED scores were  $3.1 \pm 1.7$  and  $1.5 \pm 1.0$ , respectively. Females had a significantly higher  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score than males ( $3.8 \pm 1.5$  vs  $2.6 \pm 1.6$ ,  $p < 0.001$ ). Compared with males, females tended to be older, to be more symptomatic, and to have a shorter duration of NVAF from diagnosis. Females were also more likely to have more permanent type of NVAF, to less commonly have CAD, to be less likely to smoke, to have less antiplatelet use and to have more hypertension, cardiac implantable electronic device and use of OAC compared with males. The rate of OAC in female and male were 78.3% and 73.3%, respectively ( $p = 0.001$ ). We performed propensity score matching to adjust for the baseline differences between male and female. There were 1044 patients of male and female after the propensity score matching. Baseline characteristics of male and female patients of propensity score matching are shown in [table 1](#). There were no significant differences between male and female for propensity score matching dataset.

### Rate of clinical outcome

The average follow-up time was  $25.7 \pm 10.6$  months or 7192.6 person-years. Ischaemic stroke/TIA, major bleeding, ICH, heart failure and death occurred in 103 (3.0%), 152 (4.5%), 50 (1.5%), 218 (6.4%) and 271 (8.0%) of patients, respectively, for an event rate and 95% CI of 1.43 (1.17 to 1.74), 2.11 (1.79 to 2.48), 0.70 (0.52 to 0.92), 3.03 (2.64 to 3.46) and 3.77 (3.33 to 4.25) per 100 person-years, respectively. [Table 2](#) shows the incidence rate of clinical outcomes according to gender for the whole dataset and propensity score matching dataset.

Ischaemic stroke/TIA and heart failure were more common in females, whereas major bleeding was more common in males for the whole dataset and propensity score matching dataset ([figure 1A,B](#)). Among the 152 patients with major bleeding during the 3-year follow-up, ICH was the most common type of major bleeding (50 cases or 32.9% of all major bleeding). The death outcome was not significantly different between males and females.

### Kaplan-Meier graph

[Figure 2A](#) shows the cumulative event rate for ischaemic stroke/TIA, major bleeding, heart failure and death compared between males and females with the adjustment of potential confounders, that is, age, type of atrial fibrillation, history of heart failure, history of CAD, diabetes mellitus, hypertension, dyslipidaemia, smoking, renal replacement therapy, history of bleeding, anticoagulant use and antiplatelet use. Female had a significantly higher rate of ischaemic stroke/TIA and heart failure, and male had a higher rate of major bleeding. [Figure 2B](#) shows cumulative event rate of clinical outcomes of the propensity score matching dataset which demonstrated the similar findings as the whole dataset.

### Linear regression analysis

Univariate and multivariate analysis of the whole dataset and propensity score matching dataset for association between gender and ischaemic stroke/TIA, major bleeding, ICH, heart failure and death is shown as a forest plot in [figure 3A,B](#). The unadjusted and adjusted HRs (and their 95% CIs) showed a similar trend for all clinical outcomes when compared between the two genders. Potential confounders that were included in the multivariate model were age, types of NVAF and comorbid conditions (hypertension, diabetes, smoking, dyslipidaemia, history of heart failure, CAD, history of ischaemic stroke, bleeding and renal replacement therapy) and medications (OAC and antiplatelet). The results of multivariate analysis revealed a higher risk of ischaemic stroke/TIA and heart failure in females, and a higher risk of major bleeding and ICH in males. Results of the propensity score matching dataset showed the similar findings.

### Effect of OAC

To adjusted for the differences in baseline characteristics in OAC and non-OAC group, we performed 2:1 propensity score matching of OAC and non-OAC group. There were 558 patients in OAC group and 274 patients in non-OAC group after the propensity score matching. OAC reduced the risk of ischaemic stroke/TIA both in female and male. However, OAC increased the risk of major bleeding and ICH in males, but only slightly increased those risks in females ([figure 4A](#)). However, warfarin was used in 91.1% of those who were on OAC. To adjusted for the differences in baseline characteristics in warfarin and NOAC group, we performed 2:1 propensity score matching of warfarin and NOAC group. There were 422 patients in warfarin group and 211 patients in NOAC group after the

**Table 1** Baseline characteristics before-and-after propensity score matching

Data	Before matching			After matching		
	Female (n=1422)	Male (n=1980)	P value	Female (n=1044)	Male (n=1044)	P value
Age (years)	69.3±10.6	66.0±11.6	<b>&lt;0.001</b>	67.87±10.58	67.80±10.83	0.882
Time after AF diagnosis (years)	3.1±4.0	3.5±4.6	<b>0.003</b>	3.17±3.96	3.30±4.20	0.462
Atrial fibrillation			<b>&lt;0.001</b>			0.934
Paroxysmal	546 (38.4%)	602 (30.4%)		363 (34.8%)	355 (34.0%)	
Persistent	243 (17.1%)	400 (20.2%)		168 (16.1%)	170 (16.3%)	
Permanent	633 (44.5%)	978 (49.4%)		513 (49.1%)	519 (49.7%)	
Symptomatic AF	1138 (80.0%)	1480 (74.7%)	<b>&lt;0.001</b>	811 (77.7%)	817 (78.3%)	0.751
History of heart failure	367 (25.8%)	545 (27.5%)	0.265	239 (22.9%)	261 (25.0%)	0.259
History of CAD	184 (12.9%)	363 (18.3%)	<b>&lt;0.001</b>	139 (13.3%)	134 (12.8%)	0.746
Having a CIED	166 (11.7%)	175 (8.8%)	<b>0.007</b>	113 (10.8%)	99 (9.5%)	0.476
History of ischaemic stroke/TIA	237 (16.7%)	355 (17.9%)	0.338	162 (15.5%)	170 (16.3%)	0.632
Hypertension	1034 (72.7%)	1294 (65.4%)	<b>&lt;0.001</b>	721 (69.1%)	739 (70.8%)	0.390
Diabetes mellitus	372 (26.2%)	467 (23.6%)	0.086	250 (23.9%)	231 (22.1%)	0.323
Current smoker	36 (2.5%)	642 (32.4%)	<b>&lt;0.001</b>	36 (3.4%)	36 (3.4%)	1.000
Dyslipidaemia	796 (56.0%)	1119 (56.5%)	0.755	583 (55.8%)	594 (56.9%)	0.627
Renal replacement therapy	12 (0.8%)	28 (1.4%)	0.128	10 (1.0%)	13 (1.2%)	0.529
Dementia	14 (1.0%)	15 (0.8%)	0.478	7 (0.7%)	4 (0.4%)	0.364
History of bleeding	148 (10.4%)	175 (8.8%)	0.123	80 (7.7%)	83 (8.0%)	0.807
CHA <sub>2</sub> DS <sub>2</sub> -VASc score (no sex)			<b>&lt;0.001</b>			0.489
- 0	91 (6.4%)	196 (9.9%)		88 (8.4%)	95 (9.1%)	
- 1	215 (15.1%)	331 (16.7%)		178 (17.0%)	159 (15.2%)	
- ≥2	1116 (78.5%)	1453 (73.4%)		778 (74.5%)	790 (75.7%)	
HAS-BLED score			0.610			0.875
0	199 (14.0%)	291 (14.7%)		170 (16.3%)	170 (16.3%)	
1–2	1005 (70.7%)	1368 (69.1%)		734 (70.3%)	126 (69.5%)	
≥3	218 (15.3%)	321 (16.2%)		140 (13.4%)	148 (14.2%)	
Antiplatelet	315 (22.2%)	575 (29.0%)	<b>&lt;0.001</b>	228 (21.8%)	250 (23.9%)	0.252
Anticoagulant	1114 (78.3%)	1452 (73.3%)	<b>0.001</b>	817 (78.3%)	190 (75.7%)	0.161
Warfarin	1016 (71.4%)	1322 (66.8%)	<b>0.004</b>	743 (71.2%)	719 (68.9%)	0.252
NOACs	98 (6.9%)	130 (6.6%)	0.708	74 (7.1%)	71 (6.8%)	0.796

Data presented as mean±SD or number and n (percentage).

A p<0.05 indicates statistical significance (bold and italic).

AF, atrial fibrillation; CAD, coronary artery disease; CIED, cardiac implantable electronic device; NOACs, non-vitamin K antagonist oral anticoagulants; TIA, transient ischaemic attack.

2:1 propensity score matching. Compared with warfarin, male patients on NOACs had a lower rate of ischaemic stroke/TIA and major bleeding than female patients (figure 4B). However, since the number of patients who received NOAC was small, the comparison for the effect of warfarin vs NOAC had a limited power. Among the 2233 patients who had enough international normalised ratio (INR) data to calculate the time in therapeutic range (TTR), the average TTR was 53.6%±26.4%. TTR was not significantly different between males and females

(53.1±26.1 vs 54.1%±26.7%, p=0.376). There was also no significant difference between males and females for time below TTR (32.5%±27.6% vs 31.5±27.8%, p=0.421) or time above TTR (14.0%±17.3% vs 14.2±17.8%, p=0.841). The rate of OAC use was significantly higher in females than in males (78.3% vs 73.3%, p=0.001); however, there was no difference between genders for the rate of NOAC use.

We rerun analysis for the effect of OAC in male and female with the adjustment of age, type of atrial

**Table 2** Rate of clinical outcomes according to gender for the whole dataset and propensity score matching

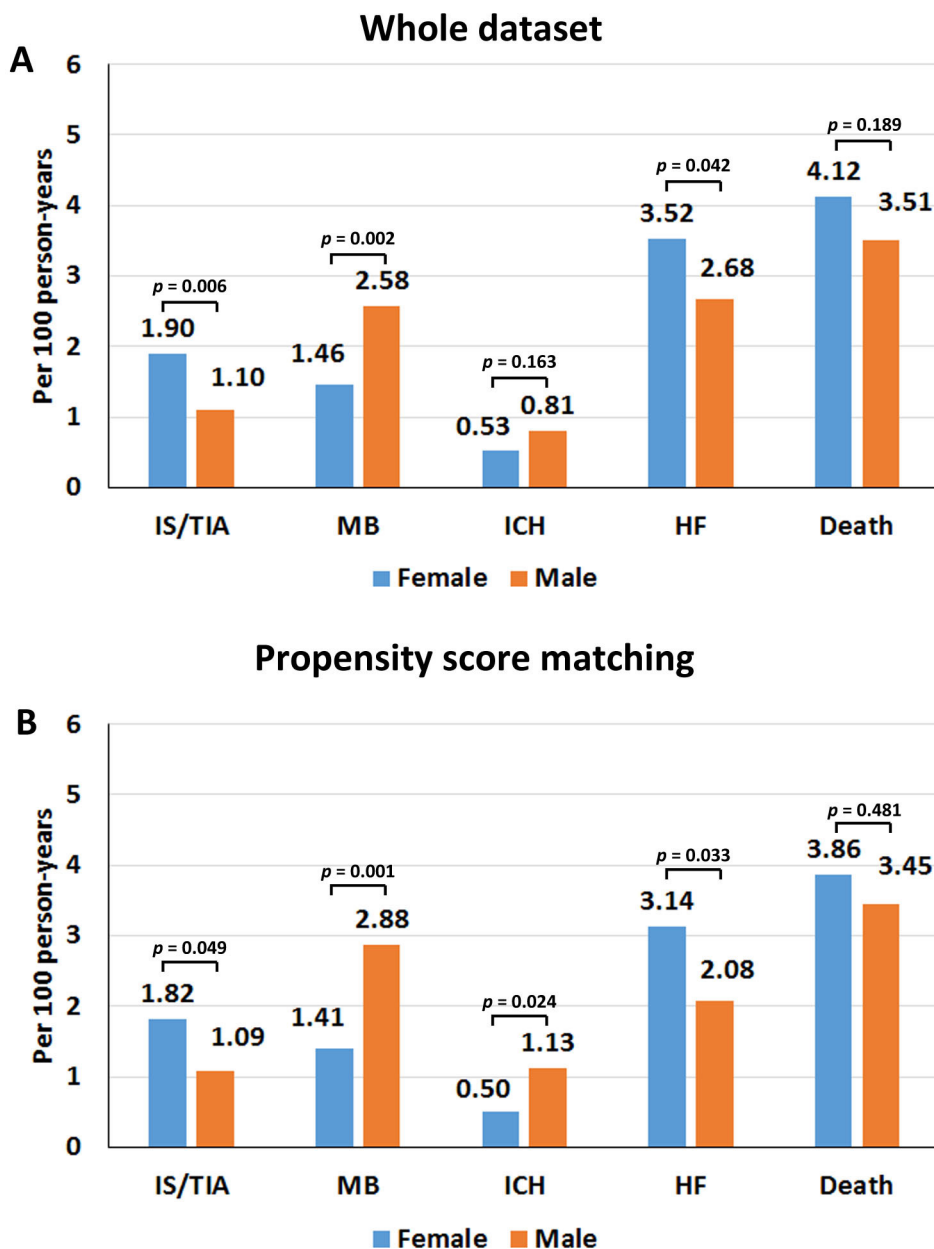
Gender	No of patients	No of events	100 person-years	Rate per 100 person-years (95% CI)
Whole dataset				
Ischaemic stroke/TIA				
Male	1422	46	41.8	1.10 (0.81 to 1.47)
Female	1980	57	30.1	1.90 (1.43 to 2.45)
Major bleeding				
Male	1422	108	41.8	2.58 (2.12 to 3.12)
Female	1980	44	30.1	1.46 (1.06 to 1.96)
ICH				
Male	1422	34	41.8	0.81 (0.56 to 1.14)
Female	1980	16	30.1	0.53 (0.30 to 0.86)
Heart failure				
Male	1422	112	41.8	2.68 (2.21 to 3.22)
Female	1980	106	30.1	3.52 (2.88 to 4.26)
Death				
Male	1422	147	41.8	3.51 (2.97 to 4.13)
Female	1980	124	30.1	4.12 (3.43 to 4.91)
Propensity score matching				
Ischaemic stroke/TIA				
Male	1044	23	21.2	1.09 (0.69 to 1.63)
Female	1044	40	22.0	1.82 (1.30 to 2.48)
Major bleeding				
Male	1044	63	21.2	2.98 (2.28 to 3.80)
Female	1044	31	22.0	1.41 (0.96 to 2.00)
ICH				
Male	1044	24	21.2	1.13 (0.42 to 1.68)
Female	1044	11	22.0	0.50 (0.25 to 0.89)
Heart failure				
Male	1044	44	21.2	2.08 (1.51 to 2.79)
Female	1044	69	22.0	3.14 (2.44 to 3.97)
Death				
Male	1044	73	21.2	3.45 (2.70 to 4.33)
Female	1044	83	22.0	3.77 (3.01 to 4.68)

ICH, intracerebral haemorrhage; TIA, transient ischaemic attack.

fibrillation, history of heart failure, history of CAD, diabetes mellitus, hypertension, dyslipidaemia, smoking, renal replacement therapy, history of bleeding, anticoagulant use and antiplatelet use. The results showed that OAC had significant effect in ischaemic stroke reduction in female (HR 0.46, 95% CI 0.27 to 0.80,  $p=0.006$ ) but not in male (HR 0.78, 95% CI 0.33 to 1.81,  $p=0.559$ ). OAC significantly increased risk of major bleeding in male (HR 3.33, 95% CI 1.67 to 6.66,  $p=0.001$ ), but not in female (HR 1.79, 95% CI 0.65 to 4.94,  $p=0.260$ ). OAC also significantly increased risk of ICH in male (HR 4.71, 95% CI 1.11 to 19.95,  $p=0.036$ ), but not in female (HR 2.36, 95% CI 0.34 to 16.36,  $p=0.384$ ).

### Sensitivity analysis

To make more homogeneous cohort, we performed additional analysis by comparing effect of gender on clinical outcomes by remove patients who were on NOACs. We also analyse effect OAC on clinical outcome in male and female by removing NOAC data. The results of adjusted HR and 95% CI of the three clinical outcomes were preserved at HR and 95% CI of 1.54 (1.04 to 2.29),  $p=0.033$ , 1.63 (95% CI 1.19 to 2.24),  $p=0.002$  for the increased risk of female for ischaemic stroke/TIA and heart failure, and 1.89 (95% CI 1.32 to 2.70),  $p=0.001$  for the increased risk of male for major bleeding.



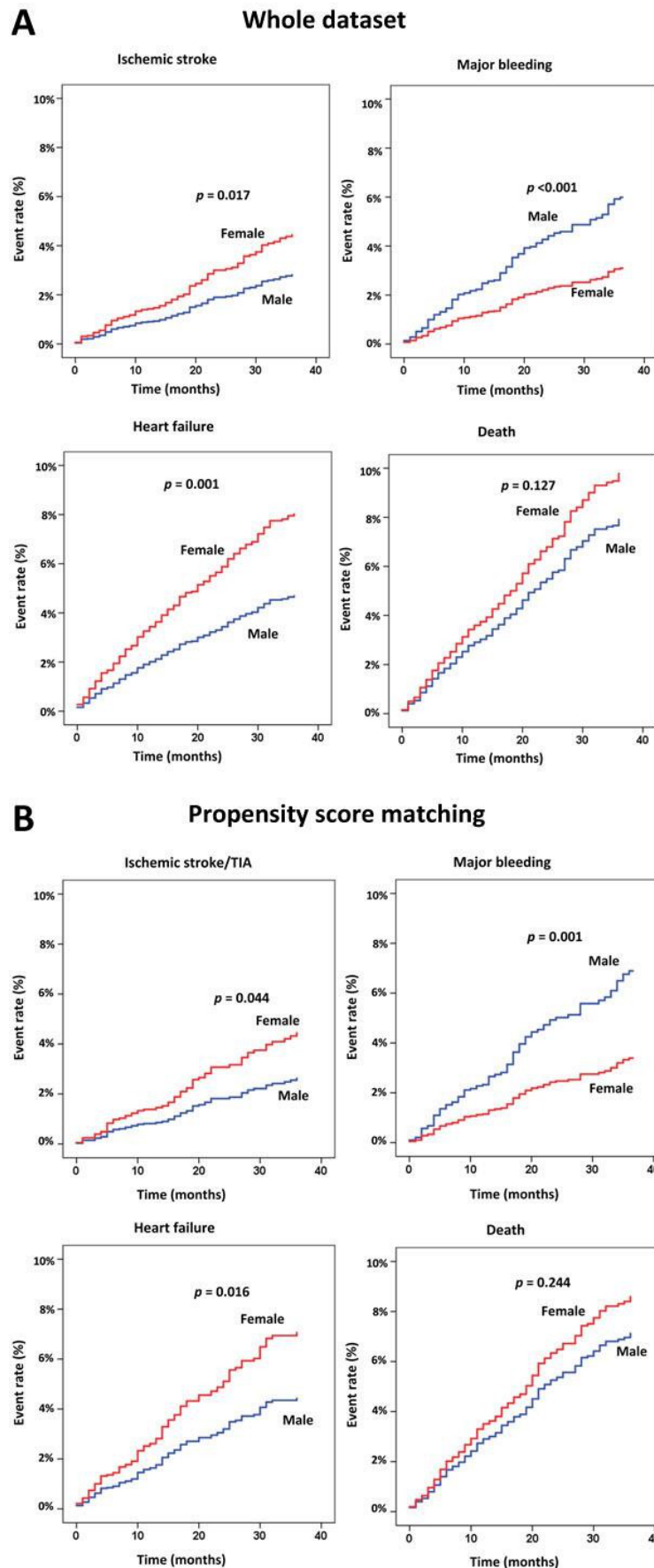
**Figure 1** Rate of ischaemic stroke (IS)/transient ischaemic attack (TIA), major bleeding (MB), intracerebral haemorrhage (ICH), heart failure (HF) and death in females and males. (A) whole dataset. (B) propensity score matching.

The effect of OAC on ischaemic stroke/TIA and major bleeding in male and female was analysed with the removal of NOAC and adjusted for potential confounders. The results showed that warfarin significantly reduced risk of ischaemic stroke/TIA in female (HR 0.55, 95% CI 0.32 to 0.93,  $p=0.025$ ) but not in male (HR 0.82, 95% CI 0.35 to 1.90,  $p=0.642$ ). For major bleeding, warfarin significantly increased risk in male (HR 2.73, 95% CI 1.55 to 4.82,  $p=0.001$ ) but not in female (HR 0.144, 95% CI 0.71 to 2.91,  $p=0.315$ ).

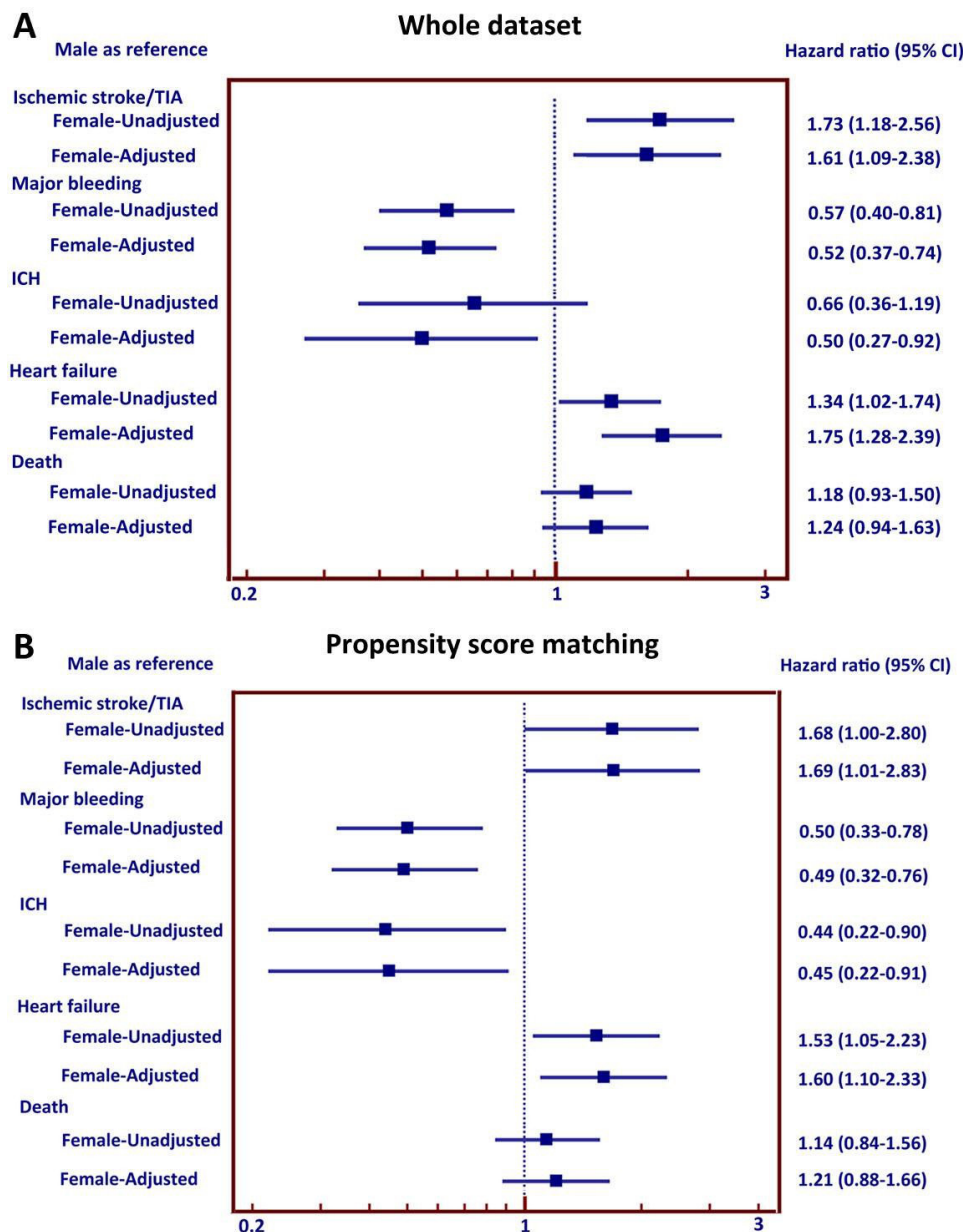
#### Net clinical benefit

We used the propensity score matching of OAC versus non-OAC and warfarin versus NOAC to calculate NCB. NCB was calculated by assigning ICH a weight of 1.5. NCB calculation was performed in all patients and in all

high-risk patients. High risk was defined as a male with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of 2 or more, and a female with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of 3 or more. Comparing OAC vs no OAC, females had a positive NCB, which means that OAC had more benefit than risk in females. In contrast, males had a negative NCB, or more risk than benefit. The NCB of OAC vs no OAC in high-risk patients was similar to that of the same analysis conducted in all patients. Even though warfarin was used in more than 90% of those who used OAC, we also decided to calculate the NCB for NOAC vs warfarin. The results of that analysis showed that NOAC had more positive NCB than OAC for both males and females, which indicates that NOAC should be a preferred OAC. However, since the rate of NOAC use was small, we should not draw any



**Figure 2** Cumulative event rate of male and female patients with non-valvular atrial fibrillation for ischaemic stroke/transient ischaemic attack (TIA), major bleeding, heart failure and death. (A) whole dataset. (B) propensity score matching.



**Figure 3** Forest plot shown as HR and 95% CI of male and female patients with non-valvular atrial fibrillation for ischaemic stroke/transient ischaemic attack (TIA), major bleeding, intracerebral haemorrhage (ICH), heart failure and death. Male gender was used as reference. (A) whole dataset (B) propensity score matching.

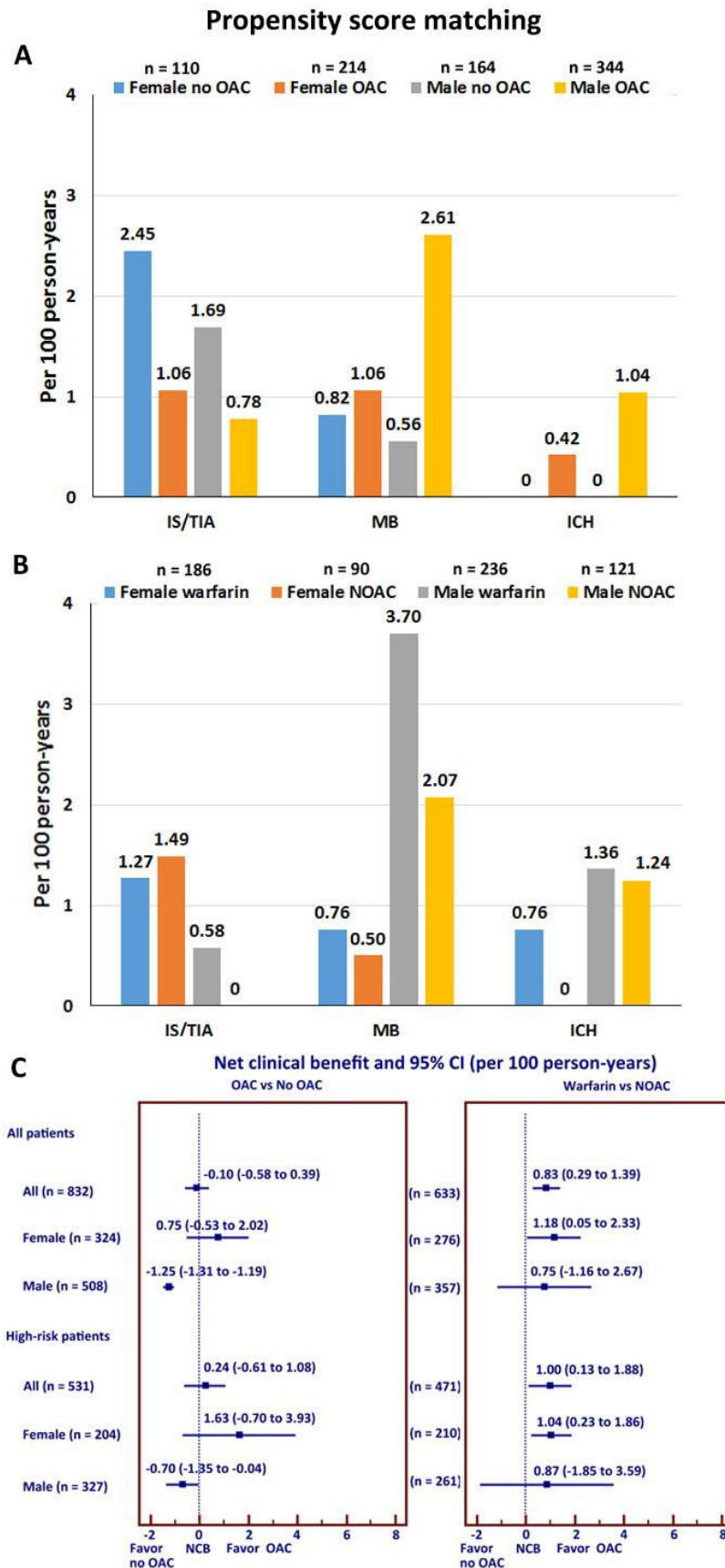
conclusions relating to the NOAC data and comparisons of this study.

## DISCUSSION

The results of this prospective nationwide multicentre NVAF registry demonstrated differences in the risk of different adverse clinical outcomes between males and females. Females had an increased risk of ischaemic stroke/TIA, whereas males had increased risk of major bleeding and ICH. Moreover, the risk of those clinical outcomes remained the same after adjustment for potential confounders. Use of OAC had benefit in females than in males, and NOAC was found to be superior to warfarin.

A review from previous data showed that female patients with NVAF had an approximately 30% increased risk of ischaemic stroke compared with males irrespective of OAC.<sup>7 15</sup> A systematic review and meta-analysis of 5 randomised controlled trials and 12 prospective observational studies from Western population demonstrated that female increased risk of ischaemic stroke related to NVAF approximately 1.29-fold.<sup>16</sup> A recent meta-analysis of 993 603 NVAF patients from 44 studies also demonstrated an increased risk of ischaemic stroke in females with a HR of 1.24.<sup>17</sup> Compared with Western population, data from Asian population are limited. The Fushimi registry reported on gender differences in the outcomes of 3878 NVAF patients from Japan with a median follow-up of 36.7





**Figure 4** Rate of ischaemic stroke (IS)/transient ischaemic attack (TIA), major bleeding (MB) and intracerebral haemorrhage (ICH) of male and female patients with non-valvular atrial fibrillation for A. Oral anticoagulant (OAC) versus no OAC; (B) Non-vitamin K antagonist oral anticoagulant (NOAC) versus warfarin and (C) Net clinical benefit of OAC versus no OAC (left), and of NOAC versus warfarin (right) in all patients, and in high-risk patients. Propensity score matching was used for A, B and C.

months.<sup>10</sup> Female gender was not an independent factor for ischaemic stroke (1.84 vs 1.57 per 100 person-years,  $p=0.282$ ); however, females had a lower rate of intracranial bleeding compared with males (0.53 vs 0.85 per 100 person-years,  $p=0.041$ ). Females also demonstrated a trend towards a lower major bleeding rate compared with males (1.64 vs 2.08 per 100 person-years,  $p=0.104$ ). The results of our study were slightly different from those of the Fushimi registry. We found female gender to be an independent risk factor for ischaemic stroke/TIA (1.90 vs 1.10 per 100 person-years,  $p=0.005$ ) after adjustment for confounding factors that included OAC use. Compared with males, we also found that females had a lower rate of major bleeding (1.46 vs 2.58 per 100 person-years,  $p=0.001$ ) and ICH (0.53 vs 0.81 per 100 person-years,  $p=0.156$ ). The overall rates of ischaemic stroke, major bleeding and ICH were similar between our study and Fushimi registry.

Data on the clinical outcomes of 17162 patients with newly diagnosed NVAf were reported from the GARFIELD study.<sup>18</sup> The rates of ischaemic stroke and major bleeding (1.25 and 0.7 per 100 person-years, respectively) from that study<sup>18</sup> are lower than the rates found in both our study and the Fushimi registry. However, Caucasians accounted for approximately 65% of the sample in the GARFIELD study. The higher rate of ischaemic stroke and major bleeding in our study may be related to a lower TTR among patients receiving warfarin in Asian population compared with other regions of the world (31.1 vs 54.1%).<sup>19</sup> However, difference in TTR cannot be used to explain the difference in ischaemic stroke and major bleeding between males and females in our study since the TTR was similar between males and females. Differences in the rates of clinical outcomes between males and females were found in 28 624 NVAf patients in the GARFIELD registry.<sup>8</sup> Females had a higher rate of ischaemic stroke (HR: 1.31), and a similar rate of major bleeding (HR: 1.13) compared with males. The reduction in ischaemic stroke with OAC was greater in males (HR: 0.45) than in females (HR: 0.77). The risk of major bleeding with OAC was slightly greater in males compared with females (HR of 2.33 for males and 1.86 for females), but the difference was not statistically significant ( $p=0.53$ ). However, the results of the GARFIELD registry are different from our study in many aspects. We found that males had a higher bleeding risk compared with females, but the GARFIELD study found the major bleeding rate to be similar with an HR of 1.13 for female gender.<sup>8</sup> Moreover, GARFIELD reported a greater reduction in ischaemic stroke among males on OAC compared with females, but we found a greater reduction in females than in males in our study. Data from a national database of patients with NVAf in both Western population<sup>11</sup> (N=239671) and Taiwanese population<sup>20</sup> (N=59583) showed that female gender increased the risk of stroke only in older adults, and both challenged the gender category component of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The rate of OAC and antiplatelet use in female and male was not different in GARFIELD

study.<sup>21</sup> However, in our study, female had a higher rate of OAC use (78.3% vs 73.3%,  $p=0.001$ ) and lower rate of antiplatelet use (22.2% vs 29.0%,  $p<0.001$ ). The higher rate of OAC use in female may be related to the higher risk of stroke and higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score in female. The higher rate of antiplatelet use in male could be due to the higher rate of CAD in male.

A population-based cohort study in Canada that included 147 622 NVAf patients, and that employed time-fixed adjustment for confounders showed that females had a slightly higher rate of ischaemic stroke compared with males.<sup>22</sup> Using age-matched and time-matched nested case-control analysis, the risk of ischaemic stroke was not found to be significantly different between males and females. However, that study used data from a computerised database that covered a 10-year period (2000–2009), which means that there might be some treatment effect over time that was not included in their list of potential confounders. In contrast, the present study used a computerised database consisting of prospective primary outcome data that was validated via an adjudication process that we established for this study. Our study did agree with the Canadian study relative to a higher rate of major bleeding being found in males than in females.

In our study, OAC significantly reduced ischaemic stroke/TIA risk in female (6.5% for no OAC and 3.3% for OAC,  $p=0.012$ ) but not for male (2.5% for no OAC and 2.3% for OAC,  $p=0.805$ ). The possible explanations were (1) the risk of ischaemic stroke/TIA for male is not high to start with, which is 1.1 per 100 person-years compared with 1.90 (1.43–2.45) for female. Therefore, it was difficult to demonstrate the benefit of OAC in non-high risk group, (2) warfarin accounted for 91.1% of those who were on OAC in our study. As demonstrated in the meta-analysis, NOACs were superior to warfarin for the reduction of ischaemic stroke with the risk reduction of 19% ( $p<0.0001$ ),<sup>23</sup> (3) In our study, for those who were on warfarin, the INR was substandard. Average TTR was 53.6%±26.4%. Guideline recommended that TTR should be at least 70% for those who are on warfarin.<sup>2</sup> A previous study demonstrated that NVAf with warfarin treatment and TTR greater than 70% had a significant reduction in ischaemic stroke compared with the suboptimal TTR group.<sup>24</sup> Although TTR was not different between male and female in our study (53.1±26.1 vs 54.1±26.7%,  $p=0.376$ ), the suboptimal TTR in combination with low NOAC use and relatively low stroke risk in male group in our study together explain the non-significant reduction in ischaemic stroke in male with OAC in our study. Besides, in our study, history of CAD and smoking were more common in male. Therefore, male had an increase chance of having ischaemic stroke that is related to atherosclerotic process of the carotid system even in the setting of NVAf.<sup>25</sup> As a result, OAC may have little impact in the stroke reduction in this setting.

The rate of ICH in our study was 0.7% per year. This is similar to the rate of ICH reported in Asian population.<sup>26</sup>

The overall rate of ICH from NOAC trials was 0.3%–0.6%.<sup>27–29</sup> Asian population increased the risk of ICH at the HR of 3.19 compared with European patients in Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study<sup>29</sup> and 2.02 in Rivaroxaban Once Daily Oral DirectFactor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study.<sup>27</sup> Therefore, the rate of ICH in Asian population from previous studies was similar to ours. A previous report that showed an increased risk of ICH in Asian population of 4 folds compared with Caucasian demonstrated that the rate of ICH in Asian population from warfarin was 1.75% per year.<sup>30</sup> A review article summarised that the rate of ICH in Asian population was 1.1%–2.5% per year and at least twice higher than Caucasians.<sup>31</sup> The possible reasons may be (1) poor TTR control which could increase the risk of both major bleeding and ischaemic stroke, (2) extensive use of herbal medicine and pain medication from the over-the-counter, (3) limited access of warfarin clinic and (4) genetic predisposition.<sup>31</sup>

There are some possible explanations for the increased risk of ischaemic stroke in females. Female had frequent fluctuations of prothrombotic activity which may be related to oral contraceptives, menstrual cycles, pregnancy, menopause and hormone replacement therapy.<sup>32</sup> Female hormone may have effect on intrinsic coagulation cascade (especially Factor XII), and may increase plasminogen activator inhibitor,<sup>33</sup> which also helps to explain the lower rate of major bleeding in females. Females may have a lower rate of OAC and poorer OAC control, which may be related to a perception that females have a higher rate of bleeding.<sup>34 35</sup> Male may increase risk of bleeding from a more aggressive antithrombotic treatment and more frequent use of combination of OAC and antiplatelet,<sup>8 32</sup> which has also been demonstrated in our study.

We also demonstrated that females have an increased risk for heart failure. Previous study reported that females had more atrial remodelling, which may be related to a differential effect on gene and protein expression causing fibrotic and electrical remodelling on the atria.<sup>34</sup> Increased atrial scarring in females was observed by late gadolinium enhancement MRI.<sup>36</sup> Females with NVAf had an increased risk of heart failure compared with males, especially heart failure with preserved ejection fraction.<sup>37</sup> Females also had more microvascular dysfunction compared with males.<sup>37</sup> The Fushimi registry also demonstrated an increased risk of heart failure in females with NVAf (4.25 vs 3.01 per 100 person-years,  $p=0.001$ ).

Our study has some limitations. First, majority of the participating hospitals were large hospitals. The results may not be generalised to all hospital setting. Second, majority of OAC use in this study was warfarin. The results may not be applied to the area with high use of NOACs. The major reasons for the high rate of warfarin use in our study was related to the policy of the reimbursement

systems of our country to save cost of the expensive medications. They promote the use of warfarin as the first choice of OAC. To use NOACs, physicians needs to provide the reason for use in the drug utilisation evaluation form. Third, based on the formula used to calculate NCB that has been described in the original paper,<sup>14</sup> the formula did not allow for the adjustment of factors that might affect the clinical outcomes. The formula was based on the rate of ischaemic stroke/TIA and ICH of patients with OAC versus no OAC and weight ICH as 1.5.

## CONCLUSION

Female gender was found to be associated with increased risk of ischaemic stroke/TIA—even after correction for potential confounders, including OAC. Male gender demonstrated association with increased risk of major bleeding. OAC showed benefit mainly in females; however, the superiority of NOAC over warfarin was shown in both males and females.

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