

# Renal outcomes in Asian patients receiving oral anticoagulants for non-valvular atrial fibrillation

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## ABSTRACT

**Introduction:** Patients with non-valvular atrial fibrillation (NVAF) may be prescribed warfarin or a non-vitamin K oral anticoagulant (NOAC). There is increasing evidence that NOACs are superior to warfarin in terms of renal function preservation. This study aimed to compare renal outcomes in Chinese patients with NVAF between patients receiving NOACs and patients receiving warfarin.

**Methods:** In total, 600 Chinese patients with NVAF receiving oral anticoagulant therapy were retrospectively identified from an administrative database. The renal outcomes ( $\geq 30\%$  decline in estimated glomerular filtration rate [eGFR], doubling of serum creatinine, and kidney failure) were compared among four propensity-weighted treatment cohorts (warfarin,  $n=200$ ; rivaroxaban,  $n=200$ ; dabigatran,  $n=100$ ; and apixaban,  $n=100$ ).

**Results:** The mean follow-up period across all groups was  $1000 \pm 436$  days. Compared with warfarin, the three NOACs (pooled for consideration as a single unit) had significantly lower risks of  $\geq 30\%$  decline in eGFR (hazard ratio [HR]=0.339;

95% confidence interval [CI]=0.276-0.417) and doubling of serum creatinine (HR=0.550; 95% CI=0.387-0.782). Dabigatran and rivaroxaban users both had lower risks of  $\geq 30\%$  decline in eGFR (both  $P<0.001$ ) and doubling of serum creatinine (both  $P<0.05$ ). Apixaban was only significantly associated with a lower risk of  $\geq 30\%$  decline in eGFR ( $P<0.001$ ).

**Conclusions:** Compared with warfarin, NOACs may be associated with a significantly lower risk of decline in renal function among Chinese patients with NVAF.

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### New knowledge added by this study

- Decline in kidney function is common among Chinese patients who receive oral anticoagulant treatment for non-valvular atrial fibrillation.
- Warfarin usage is associated with significant long-term decline in renal function among patients treated for non-valvular atrial fibrillation.
- Compared with warfarin, non-vitamin K oral anticoagulant (NOAC) usage may be associated with a reduced risk of long-term decline in renal function among Chinese patients.

### Implications for clinical practice or policy

- Patients receiving oral anticoagulants, especially warfarin, should undergo close renal function monitoring during the course of treatment.
- Considering that the decline in renal function may be more accelerated in warfarin users than in NOAC users, clinicians may consider preferential use of NOACs for anticoagulant therapy, especially in patients with existing renal impairment or risk factors for future decline in renal function.
- The inconsistencies of NOAC prescribing patterns with drug labelling in routine clinical practice should receive greater attention because dose reduction in the absence of a renal indication may reduce treatment effectiveness without providing a greater safety benefit.

## Introduction

Various randomised controlled trials have demonstrated that non-vitamin K oral anticoagulants (NOACs), including factor Xa and direct thrombin inhibitors, are superior to warfarin, a vitamin K antagonist, in terms of efficacy and safety for preventing stroke and systemic thromboembolisms in patients with non-valvular atrial fibrillation

(NVAF).<sup>1-4</sup> The superiority of NOACs compared with warfarin appears to be consistent across ethnic groups, including Asian populations.<sup>5</sup> Furthermore, data from two sub-studies of the NOAC trials<sup>6,7</sup> and a real-world cohort study<sup>8</sup> suggested that NOACs may also be superior to warfarin in terms of maintaining and preserving renal function. A US-based cohort study demonstrated a lower

## 非瓣膜性心房顫動的亞洲患者接受口服抗凝血藥治療的腎臟結局

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**引言：**非瓣膜性心房顫動（NVAF）患者可獲處方華法林或非維他命K口服抗凝血藥（NOAC）。越來越多證據表明NOAC比華法林更有效保護腎臟功能。本研究旨在比較服用NOAC患者和服用華法林患者對腎臟結局的影響。

**方法：**從行政數據庫中追溯600名接受口服抗凝血藥治療的華籍NVAF患者，分為四個傾向加權治療隊列（華法林200例、利伐沙班200例、達比加群100例、阿哌沙班100例）比較腎臟功能（即估算的腎小球濾過率eGFR下跌30%或以上、血清肌酐加倍及腎衰竭）。

**結果：**整體的平均隨訪時間為1000 ± 436天。與華法林組相比，三組NOAC（合併為一個組別考慮）eGFR下跌30%或以上風險（風險比0.339；95%置信區間=0.276-0.417）以及血清肌酐加倍的風險均較低（風險比0.550；95%置信區間=0.387-0.782）。達比加群和利伐沙班組eGFR下跌30%或以上風險（兩者均P<0.001）和血清肌酐加倍的風險均明顯較低（兩者均P<0.05）。阿哌沙班僅與eGFR下跌30%或以上的風險較低顯著相關（P<0.001）。

**結論：**與華法林相比，NOAC可能與華籍NVAF患者腎功能下降風險顯著降低相關。

risk of decline in renal function among patients receiving NOACs than among patients receiving warfarin.<sup>8</sup> Moreover, findings from the ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and RE-LY (Randomized Evaluation of Long Term Anti-coagulation Therapy) trials revealed more rapid estimated glomerular filtration rate (eGFR) decline in patients receiving warfarin than in patients receiving rivaroxaban and dabigatran, respectively.<sup>6-8</sup> Further studies have demonstrated that warfarin treatment may be associated with more rapid progression of chronic kidney disease and can cause acute kidney injury.<sup>8-10</sup> This decline in renal function has been attributed to a phenomenon known as ‘warfarin-related nephropathy’, which is associated with vitamin K antagonism and excessive anticoagulation.<sup>8,9,11</sup> In contrast, NOACs may offer renovascular protection through pharmacological mechanisms such as the inhibition of thrombin and factor Xa.<sup>8,12,13</sup>

Differences in the pharmacological actions of warfarin and NOACs are reflected in the growing research that suggests NOACs are more effective than warfarin for preserving renal function.<sup>8,14</sup> Considering that Asian warfarin users tended to have a lower time in therapeutic range (TTR)<sup>15,16</sup> of the international normalised ratio (INR), which is associated with decline in renal function,<sup>6,14</sup> the

renal effects of NOACs compared with warfarin may differ from the effects in non-Asians. Dosage prescription patterns, such as the frequency of low-dose NOAC prescriptions, also vary between Asian and non-Asian populations<sup>14,17,18</sup>; this may also affect renal outcomes because the renal effects of NOACs appear to be dose-dependent.<sup>14,19</sup> Furthermore, because of differences in NOAC-related bleeding risk between Asian and non-Asian populations, the renal protection effects of NOACs may also vary; major bleeding can cause decline in renal function.<sup>5,14,20,21</sup> To our knowledge, there remain limited data comparing NOACs to warfarin in terms of decline in renal function among Asian patients. In this study, we sought to assess the renal outcomes of an ethnic Chinese patient population with NVAF who received NOACs (ie, apixaban, dabigatran, and rivaroxaban) compared with patients who received warfarin.

## Methods

### Study design

This retrospective cohort study included four study groups: warfarin, apixaban, dabigatran, and rivaroxaban. Each NOAC was compared with warfarin.

### Study population

Data were extracted from patients’ electronic medical records in the Prince of Wales Hospital of Hong Kong. In total, 2346 consecutive patients with a prescription of warfarin or one of the three NOACs (apixaban, rivaroxaban, and dabigatran) in our hospital were screened for eligibility for this analysis. Inclusion criteria were: first began to receive an oral anticoagulant between 1 January 2012 and 31 December 2016, NVAF, age ≥18 years, minimum on-treatment duration of 3 months, and availability of laboratory data concerning serum creatinine at baseline and during follow-up. We excluded warfarin-experienced or NOAC-experienced patients to minimise confounding bias.<sup>8,22</sup> Other exclusion criteria were previous kidney failure, valvular atrial fibrillation,<sup>23</sup> and/or other indications for anticoagulation. A pre-study power analysis to detect a 10% difference in the incidence of ≥30% decline in eGFR between NOACs (pooled for consideration as a single unit) and warfarin revealed that the minimum sample size was 200 patients per arm (all NOACs vs warfarin). The sample size in each NOAC group was then matched to the approximate proportion of patients that were prescribed each of the three NOACs in actual clinical practice, in accordance with the preferences of local physicians. In our hospital during the study period, rivaroxaban was available earlier locally and was more frequently prescribed than the other two NOACs; apixaban

was the last NOAC to receive local approval and therefore exhibited a lower rate of prescription at the time of the study. This paper adheres to the STROBE reporting guidelines for observational studies.

## Study endpoints

We studied the three renal outcome endpoints:  $\geq 30\%$  decline in eGFR, doubling of serum creatinine, and kidney failure. Doubling of serum creatinine has been used as a surrogate endpoint when studying the progression of kidney disease in clinical trials.<sup>24</sup> Based on the findings of clinical trials and meta-analyses, the National Kidney Foundation and US Food and Drug Administration proposed that with at least 2 to 3 years of follow-up, a 30% to 40% decline in eGFR may also be regarded as a surrogate end point; thus, it has been used as a renal endpoint in previous cohort analyses.<sup>8,24</sup> Because doubling of serum creatinine and kidney failure occur late in kidney disease,  $\geq 30\%$  decline in eGFR serves as a more sensitive renal decline endpoint; this change is clinically significant regardless of a low follow-up or event rate.<sup>8,24</sup> Kidney failure is defined as eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>, long-term kidney dialysis, or kidney transplantation.<sup>8,25</sup> Efficacy outcomes were stroke (ischaemic or haemorrhagic) or systemic embolism (SE). Based on the initial dose prescribed, the prevalence of dose reduction for each NOAC (apixaban 2.5 mg twice daily, dabigatran 75 mg twice daily, and rivaroxaban 15 mg once daily) without a renal indication (eGFR  $< 30$  mL/min for apixaban and dabigatran; eGFR  $< 50$  mL/min for rivaroxaban) was assessed.<sup>26</sup>

Using the treatment initiation date as our index date, we retrieved the pretreatment creatinine value nearest to the index date as the baseline creatinine; we used this value to calculate the baseline eGFR by means of the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>8,27</sup> Hospital electronic records were used to identify co-morbidities and specific drug prescriptions within 3 months prior to the index date. Baseline HAS-BLED and CHA<sub>2</sub>DS<sub>2</sub>-VASC scores were also recorded. The TTR of patients in the warfarin cohort was calculated as the number of INRs in therapeutic range (INR=2-3) divided by the total INRs recorded for each patient during the analysed period.<sup>28,29</sup> Patients were followed up until the end of treatment, death, or when any efficacy or renal endpoint(s) were reached.

## Statistical analysis

For minimisation of potential confounding, we used inverse probability of treatment weighting (IPTW) to balance identified covariates.<sup>8,14,17,30</sup> Generalised boosted models were used to estimate propensity scores and weights for optimal balance

across treatment groups.<sup>31,32</sup> Weights were obtained to gather estimates representing the mean effects of treatment among treated groups.<sup>8,14</sup> Baseline characteristics (eg, patient baseline medications and pre-existing co-morbidities which may affect outcomes) were included in our model (online supplementary Table).<sup>8,14</sup> Both CHA<sub>2</sub>DS<sub>2</sub>-VASC and HAS-BLED scores were not included in the model because they are composite scores derived from other covariates.<sup>14</sup> The absolute standardised mean difference was calculated for each NOAC versus warfarin to ensure that the cohorts were sufficiently balanced before comparison of each NOAC to warfarin. An absolute standardised mean difference of  $< 0.2$  is considered balanced for each baseline covariate when comparing each NOAC to warfarin.<sup>8,31</sup> Fisher's exact test was used to compare the frequencies of dose reduction without renal indication among NOACs.

Because of some extremely high or low weights in our weighted population, we truncated weights at the 1st and 99th percentiles before conducting weighted analysis.<sup>8,33</sup> We calculated hazard ratios using weighted Cox proportional hazards regression, then generated weighted Kaplan–Meier curves that compared each NOAC to warfarin. Cumulative incidences for the Kaplan–Meier curves were presented as mean percentage incidences with 95% confidence intervals. A P value of  $< 0.05$  was considered statistically significant. Predefined subgroup analysis was performed for factors potentially associated with renal outcome, including age ( $\geq 75$  or  $< 75$  years); sex; and baseline diabetes mellitus, heart failure, and eGFR ( $\geq 60$  mL/min/1.73 m<sup>2</sup> or  $< 60$  mL/min/1.73 m<sup>2</sup>).

## Results

### Cohort characteristics

We identified 600 patients with NVAf who were receiving oral anticoagulants: 200, 100, 100, and 200 patients were receiving warfarin, apixaban, dabigatran, and rivaroxaban, respectively. After IPTW, all identified baseline characteristics were balanced between warfarin and each NOAC group (Table 1). The mean follow-up duration of the overall study cohort was  $1000 \pm 436$  days. The mean follow-up durations for each NOAC group were as follows: apixaban ( $790 \pm 345$  days), dabigatran ( $1187 \pm 322$  days), and rivaroxaban ( $999 \pm 430$  days); the median follow-up durations were 806, 1416, and 1074 days, respectively. The mean TTR of the warfarin cohort was 44.3%. The frequencies of dose reduction without a renal indication for apixaban, rivaroxaban and dabigatran were 46.9%, 35.7% and 2.0%, respectively (P $< 0.001$  for dabigatran vs both apixaban and rivaroxaban).

TABLE 1. Baseline characteristics after inverse probability of treatment weighting\*

	Warfarin (n=200)	Apixaban (n=100)	Dabigatran (n=100)	Rivaroxaban (n=200)	Absolute SMD		
					Warfarin vs apixaban	Warfarin vs dabigatran	Warfarin vs rivaroxaban
Age at prescription	76.2 ± 9.0	75.8 ± 10.3	77.8 ± 7.3	76.6 ± 8.4	0.044	0.196	0.045
Female sex	46.8	55.7	51.0	49.8	0.177	0.083	0.058
HAS-BLED score	2.8 ± 1.1	2.6 ± 1.1	2.9 ± 0.9	2.6 ± 1.0	0.165	0.102	0.167
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	4.1 ± 1.7	4.1 ± 1.7	4.2 ± 1.7	4.2 ± 1.6	0.004	0.066	0.050
Heart failure	24.1	20.6	20.1	22.9	0.084	0.097	0.028
Hypertension	76.5	74.5	76.5	79.4	0.046	0.001	0.072
Diabetes mellitus	37.0	28.0	37.9	34.9	0.192	0.019	0.044
History of ischaemic stroke / TIA / systemic thromboembolism	27.7	34.7	23.2	30.2	0.151	0.104	0.055
History of bleeding	4.8	7.7	5.9	3.5	0.122	0.049	0.064
Prior myocardial infarction	17.1	20.5	16.8	17.0	0.087	0.007	0.003
History of cancer	9.3	10.7	9.6	8.8	0.048	0.013	0.016
Antiplatelet therapy	59.1	51.3	55.8	55.9	0.156	0.066	0.065
Other NSAID	4.0	5.6	5.9	1.6	0.076	0.088	0.146
Statin therapy	48.6	49.5	45.4	51.0	0.019	0.064	0.048
Diuretic therapy	33.1	29.8	33.4	27.8	0.070	0.008	0.114
ACEi / ARB / ARNi / MRA	52.6	49.9	57.0	54.2	0.053	0.090	0.032
eGFR, mL/min/1.73 m <sup>2</sup>	63.7 ± 18.8	64.1 ± 18.5	64.7 ± 16.2	64.6 ± 18.7	0.021	0.058	0.047

Abbreviations: ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitors; CHA<sub>2</sub>DS<sub>2</sub>-VASc = congestive heart failure, hypertension, age ≥75 years, age 65 to 74 years, stroke/transient ischaemic attack/thromboembolism, vascular disease, diabetes mellitus, sex (female); eGFR = estimated glomerular filtration rate; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalised ratio, elderly (age >65 years), drugs (eg, antiplatelet), or alcohol; MRA = mineralocorticoid receptor antagonists; NSAID = non-steroidal anti-inflammatory drug; SMD = standardised mean difference; TIA = transient ischaemic attack

\* Data are shown as mean ± standard deviation or %

TABLE 2. Hazard ratios with 95% confidence intervals (95% CI)

	Hazard ratio (95% CI)	P value
≥30% Decline in estimated glomerular filtration rate		
Apixaban	0.552 (0.418-0.730)	<0.001
Dabigatran	0.203 (0.144-0.285)	<0.001
Rivaroxaban	0.343 (0.260-0.451)	<0.001
Warfarin	Reference	Reference
Doubling of serum creatinine		
Apixaban	0.914 (0.566-1.474)	0.711
Dabigatran	0.525 (0.333-0.829)	0.006
Rivaroxaban	0.311 (0.180-0.536)	<0.001
Warfarin	Reference	Reference
Kidney failure		
Apixaban	1.451 (0.804-2.619)	0.217
Dabigatran	0.544 (0.268-1.105)	0.092
Rivaroxaban	0.544 (0.273-1.083)	0.083
Warfarin	Reference	Reference
All stroke (ischaemic or haemorrhagic) or systemic embolism		
Apixaban	0.803 (0.424-1.522)	0.501
Dabigatran	0.151 (0.054-0.423)	<0.001
Rivaroxaban	0.613 (0.340-1.104)	0.103
Warfarin	Reference	Reference

### Renal and efficacy outcomes

When the three NOACs were pooled for consideration as a single unit and compared with warfarin, NOAC users exhibited lower risks of ≥30% decline in eGFR (hazard ratio [HR]=0.339; 95% confidence interval [CI]=0.276-0.417; P<0.001) and doubling of serum creatinine (HR=0.550; 95% CI=0.387-0.782; P<0.001). Individual comparisons of each NOAC to warfarin (Table 2) revealed that dabigatran and rivaroxaban users both had lower risks of ≥30% decline in eGFR (both P<0.001) and doubling of serum creatinine (both P<0.05). However, apixaban users only had a lower risk of ≥30% decline in eGFR (P<0.001). Despite trends suggestive of lower kidney failure risk in patients receiving dabigatran or rivaroxaban, the overall use of NOACs was not significantly associated with lower kidney failure risk, compared with the use of warfarin. Figure 1 shows the weighted Kaplan–Meier curves for the renal endpoints. For the efficacy outcome, dabigatran was associated with a lower incidence of stroke/SE (HR=0.151; 95% CI=0.054-0.423); P<0.001 vs warfarin), whereas the use of apixaban or rivaroxaban was not significantly associated with a lower incidence of stroke/SE, compared with the use of warfarin (Fig 2).

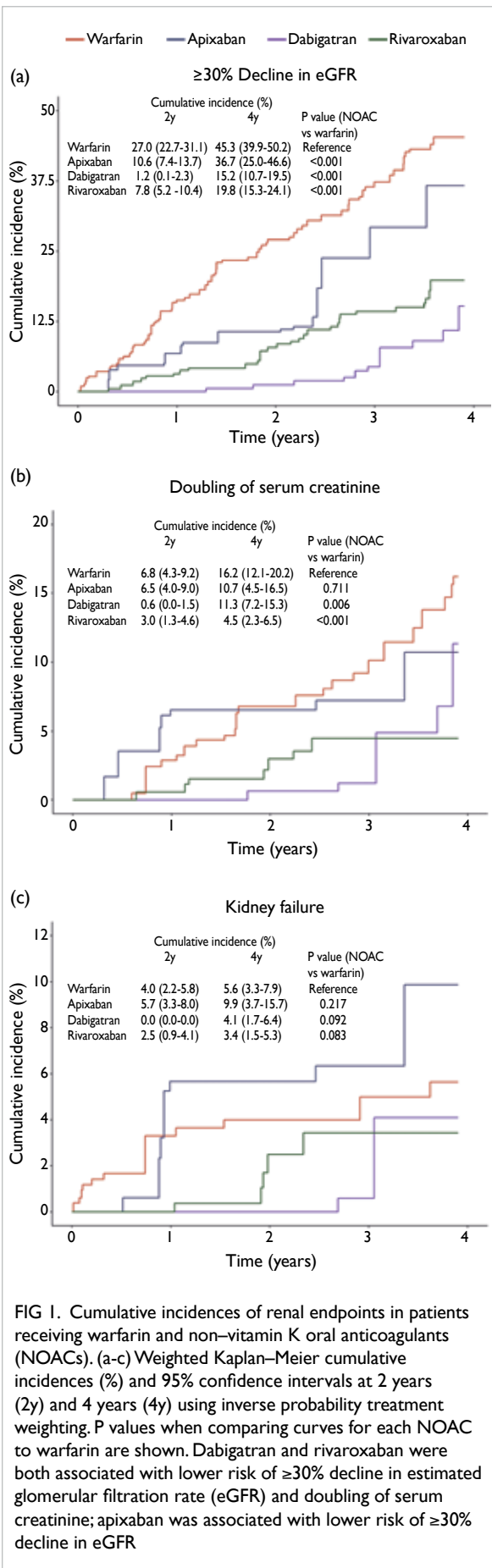


FIG 1. Cumulative incidences of renal endpoints in patients receiving warfarin and non-vitamin K oral anticoagulants (NOACs). (a-c) Weighted Kaplan-Meier cumulative incidences (%) and 95% confidence intervals at 2 years (2y) and 4 years (4y) using inverse probability treatment weighting. P values when comparing curves for each NOAC to warfarin are shown. Dabigatran and rivaroxaban were both associated with lower risk of  $\geq 30\%$  decline in estimated glomerular filtration rate (eGFR) and doubling of serum creatinine; apixaban was associated with lower risk of  $\geq 30\%$  decline in eGFR

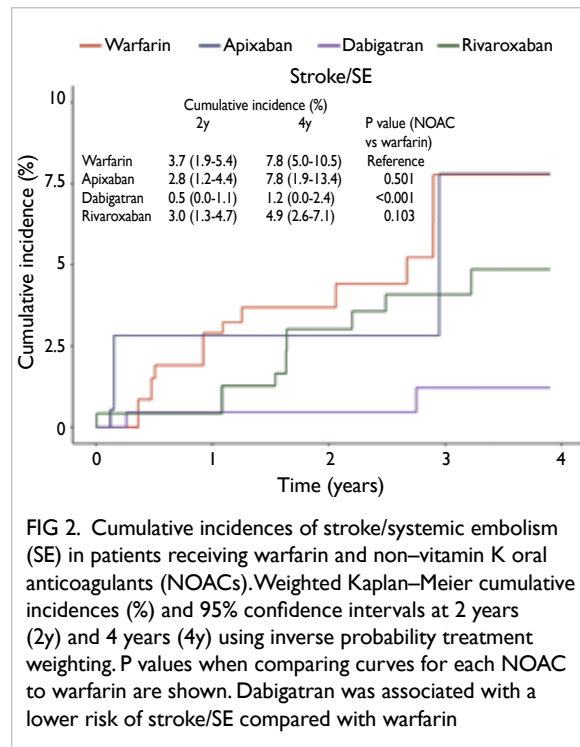


FIG 2. Cumulative incidences of stroke/systemic embolism (SE) in patients receiving warfarin and non-vitamin K oral anticoagulants (NOACs). Weighted Kaplan-Meier cumulative incidences (%) and 95% confidence intervals at 2 years (2y) and 4 years (4y) using inverse probability treatment weighting. P values when comparing curves for each NOAC to warfarin are shown. Dabigatran was associated with a lower risk of stroke/SE compared with warfarin

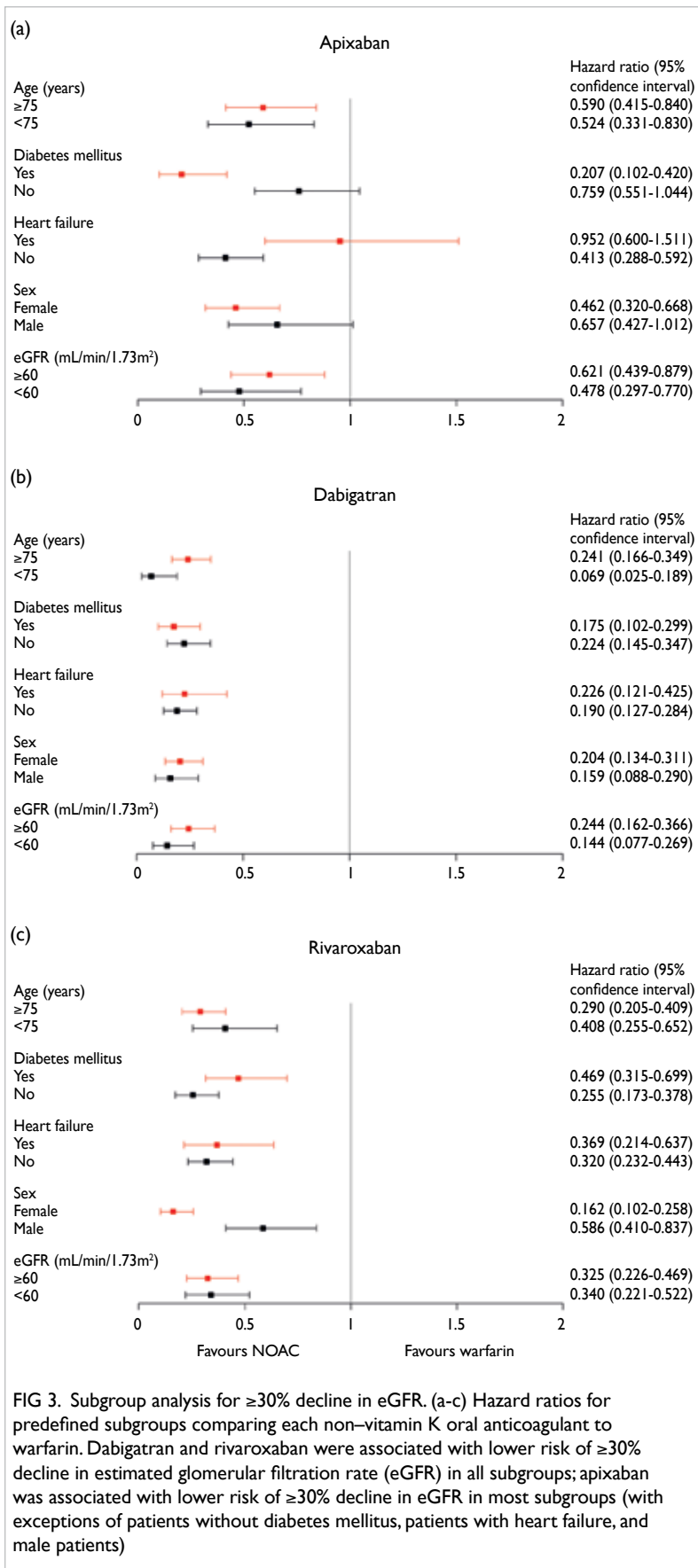
### Subgroup analysis

Analysis of the main renal endpoint,  $\geq 30\%$  decline in eGFR, consistently favoured the use of dabigatran or rivaroxaban, across all subgroups (Fig 3). However, the use of apixaban was not associated with a reduced risk of  $\geq 30\%$  decline in eGFR in three subgroups: men ( $P=0.057$ ), patients with heart failure ( $P=0.835$ ), and patients without diabetes mellitus ( $P=0.090$ ).

## Discussion

### Summary and potential mechanisms

Our cohort study provides important insights into the long-term renal impacts of NOACs versus warfarin in an ethnic Chinese population. Decline in renal function was evident among both warfarin and NOAC users in our cohort. However, the use of NOACs was generally associated with better long-term renal outcomes, compared with the use of warfarin, among Chinese patients. The general superiority of NOACs compared with warfarin was most evident for the  $\geq 30\%$  decline in eGFR surrogate endpoint. The use of dabigatran or rivaroxaban was associated with lower risks of  $\geq 30\%$  decline in eGFR and doubling of creatinine in the overall population and across predefined demographic and clinical subgroups; in contrast, the use of apixaban was not associated with a lower risk of doubling of serum creatinine in the overall population, nor was it associated with a lower risk of  $\geq 30\%$  decline in eGFR among several subgroups (men, patients without diabetes mellitus, and patients with heart failure).



Pharmacological mechanisms may explain our findings concerning NOAC superiority. Because warfarin is a vitamin K antagonist, it has inhibitory effects on matrix gamma-carboxyglutamic acid, a vitamin K-dependent protein which normally protects against vascular calcification; thus, warfarin administration potentially stimulates and accelerates the calcification of renal vascular tissue, which promotes nephropathy.<sup>8,34,35</sup> The mechanism of warfarin-related nephropathy has various contributing factors, such as the occurrence of glomerular haemorrhage and subsequent tubular injury because of red blood cell casts and haem-related free radical injury.<sup>10,36,37</sup> Alternatively, NOACs may offer renovascular protection through distinct mechanisms such as the inhibition of thrombin and factor Xa.<sup>8,12,13</sup>

### Comparison with existing literature

Our data are generally consistent with previous studies concerning the renal outcomes of NOACs versus warfarin. A study by Yao et al<sup>8</sup> regarding the renal outcomes of NOACs showed that dabigatran was associated with a lower risk of ≥30% decline in eGFR, while rivaroxaban was associated with lower risks of ≥30% decline in eGFR and doubling of serum creatinine. Analysis of the RE-LY and ROCKET AF trials similarly showed more rapid decline in eGFR among warfarin users, compared with dabigatran and rivaroxaban users.<sup>6-8</sup> Hernandez et al<sup>38</sup> demonstrated rivaroxaban superiority for adverse renal events, compared with warfarin, in patients with NVAf who had diabetes mellitus. However, our results for apixaban were inconsistent with the findings of the ARISTOTLE trial, which did not show significant apixaban superiority in terms of renal function preservation; the analysis showed similar but slightly greater decline in eGFR among apixaban users, compared with warfarin users.<sup>8,39</sup> Yao et al<sup>8</sup> also showed no clear benefits for apixaban, compared with warfarin, in terms of renal protection. Nonetheless, a study in Taiwan by Chan et al<sup>14</sup> showed that, compared with warfarin, all three NOACs were associated with lower risk for acute kidney injury in both chronic kidney disease-free and chronic kidney disease cohorts.

The differences between our findings and the results of previous studies—especially with respect to apixaban in our cohort versus the ARISTOTLE subanalysis<sup>39</sup>—may have several explanations. As mentioned by Chan et al,<sup>14</sup> Asian populations tended to have lower TTR with warfarin usage, compared with non-Asians<sup>15,16</sup>; our warfarin cohort had a mean TTR of 44.3%, which was considerably lower than findings in non-Asian populations.<sup>15,16</sup> Combined with findings that renal deterioration is greater when

warfarin is poorly controlled—especially with INR levels above the target range, as demonstrated in the RE-LY trial<sup>6</sup>—indicates that Asian populations, such as the Chinese, may have an elevated risk of warfarin-related nephropathy.<sup>14</sup> Because Asian patients may be more susceptible to renal decline associated with warfarin use, apixaban may appear superior to warfarin in Asian populations, although this superiority may not persist in non-Asian populations.<sup>8</sup> Additional apixaban superiority in Asian populations, as discussed by Chan et al,<sup>14</sup> may also be explained by the superior efficacy and safety of NOACs in Asians, compared with non-Asians.<sup>5,21</sup> Because major bleeding can be associated with renal function deterioration, the greater efficacy and safety of NOACs in Asians may facilitate renal risk reduction in such populations.<sup>5,14,21</sup> Notably, there was a high prevalence of non-guideline dose reduction without a renal indication<sup>26</sup> in the apixaban group, compared with other NOACs, in our study; this dose reduction has been associated with worse stroke prevention effectiveness and provides no safety benefit.<sup>40</sup> Nonetheless, apixaban was not significantly associated with risk reduction of the other two renal outcomes in our study, compared with warfarin. This may suggest uncertainty concerning its renal risk reduction superiority compared with warfarin. Overall, such inconsistencies across studies indicate the need for additional research; they may also reflect insufficient statistical power in our study to generate more robust conclusions.

The aforementioned findings concerning greater risk of warfarin-related nephropathy and possible lower risk of renal decline with NOAC usage in Asian populations are also potentially reflected in the comparatively lower HRs for renal endpoints in our study, compared with the US-based cohort reported by Yao et al.<sup>8</sup> When the NOACs were pooled (for consideration as a single unit) and compared with warfarin, HRs for  $\geq 30\%$  decline in eGFR and doubling of serum creatinine were both lower in our population, compared with the pooled results described by Yao et al<sup>8</sup> (HR=0.77; 95% CI=0.66-0.89 and HR=0.62; 95% CI=0.40-0.95).

### Strengths and limitations

Notable strengths of our study were its long study period and subsequent long mean follow-up duration. The longer follow-up duration, compared with previous cohort studies, indicates that previous findings concerning NOAC superiority for renal outcomes also persist during longer follow-up periods. Furthermore, our database comprised each patient's complete laboratory data; this allowed accurate recording of each renal outcome through serum creatinine and eGFR values, thus enhancing the consistency and preciseness of renal measurement across all patients. We minimised

potential confounding by only including patients who were first-time users of oral anticoagulants; this enabled us to balance numerous important baseline characteristics.

Regarding limitations, although we utilised IPTW to balance baseline covariates, confounding bias may have persisted in the study.<sup>8,14</sup> Nonetheless, we achieved balance concerning the most important identified baseline covariates that may impact renal function across treatment groups. Moreover, although the smaller number of events may have limited the statistical power with respect to the less sensitive endpoint of kidney failure, by including  $\geq 30\%$  decline in eGFR as a sensitive renal outcome, we were able to sufficiently assess early renal decline. Smaller declines in renal function (eg,  $\geq 30\%$  decline in eGFR) serve as valuable and sensitive indicators of renal decline<sup>8</sup> that has been regarded as a useful surrogate endpoint for progression to kidney failure<sup>24</sup>; it is also reportedly associated with risks of end-stage renal disease and mortality.<sup>41</sup> Frequency of testing, as mentioned in Yao et al,<sup>8</sup> may also affect results; the inclusion of patients with more follow-up creatinine tests leads to greater sensitivity concerning outcome incidence, compared with patients who underwent fewer tests. To minimise the potential impact of this sensitivity on the renal endpoints, we only included patients for whom creatinine tests were available throughout the entire follow-up period; this was possible because all patients were treated in a single centre.

Overall, the general consistency of our results with the findings of previous cohort studies, as well as the findings of the RE-LY and ROCKET AF trials, enhances the reliability and robustness of our results.<sup>6-8,14</sup> Nonetheless, further studies are needed to identify consistencies among the existing discrepancies, especially concerning apixaban. Greater certainty regarding renal outcomes of all NOACs is also important because one previous meta-analysis of various randomised controlled trials concluded that the risk of kidney failure associated with NOACs was similar to the risk associated with other anticoagulants.<sup>42</sup> Finally, although this study only involved Hong Kong Chinese patients, whose responses to NOACs and warfarin may differ from the responses of their non-Asian counterparts, the consistency of the results with findings from studies in other regions suggests widespread applicability of the findings.

### Clinical implications

In patients with NVAf who are receiving oral anticoagulants, gradual renal impairment is associated with worse clinical outcomes.<sup>39,43</sup> Our results suggested that patients receiving oral anticoagulant therapy, particularly warfarin, should undergo close renal function monitoring. Decline

in renal function during anticoagulant therapy may be less likely to occur when receiving NOACs than when receiving warfarin. The NOAC efficacy findings in this study were generally consistent with previously reported data in terms of stroke/SE prevention non-inferiority or superiority, compared with warfarin.<sup>44-47</sup> In particular, the superior efficacy of dabigatran compared with warfarin, in this local study population is reassuring. The inconsistencies of NOAC prescribing patterns with drug labelling in routine clinical practice, particularly regarding apixaban, should receive greater attention, because dose reduction in the absence of a renal indication has been associated with worse effectiveness and no safety benefit in apixaban-treated patients with normal or mildly impaired renal function.<sup>40</sup>

## Conclusions

Compared with warfarin, NOAC treatment may be associated with a lower risk of renal decline in Chinese populations; this should be considered by clinicians during the selection of anticoagulant treatment. Further studies are needed in Asian populations (eg, Chinese) to better understand the renal superiority or inferiority of NOACs compared with warfarin. Besides, NOAC-to-NOAC comparisons are needed to inform treatment selection. Additional research is needed in specific populations, such as patients with diabetes mellitus or heart failure, to better understand the impacts of baseline co-morbidities on renal risk reduction related to the use of NOACs, compared with the use of warfarin. Large-scale studies should also investigate how dosage patterns may influence renal outcomes.

## Author contributions

Concept or design: APW Lee.

Acquisition of data: All authors.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: APW Lee.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

## Conflicts of interest

APW Lee has received research grants from Bayer, Pfizer, and Boehringer Ingelheim.

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## Ethics approval

The study was approved by The Joint Chinese University of

Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref CREC 2019.405). Informed consent was waived because of the retrospective nature of this study.

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