



# The change of renal functions after nonvitamin K oral anticoagulants in patients with atrial fibrillation



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## ABSTRACT

Oral anticoagulants decreased stroke and mortality in atrial fibrillation patients. There have been cumulative data suggesting that some oral anticoagulants may exert favorable renal outcomes. The aim of this study is to evaluate the renal outcomes in patients with atrial fibrillation who took oral anticoagulant. **Methods:** A Retrospective cohort study using hospital electronic database. Serum creatinine and GFR were collected at baseline and at 1 and 2 years.

**Results:** Authors identified 734 patients with non-valvular AF who took oral anticoagulants. At the end of 2-year, the cumulative risk of significant GFR decline (eGFR drop > 30%) was 10.94% in warfarin group and 9.69% in NOACs group. The incidence rate of significant eGFR decline were comparable between NOACs and warfarin group which were 4.82 and 5.34 per 100-patient year respectively (HR 1.01 CI 0.62–1.66, p-value 0.964). However, the adjusted mean eGFR change per year was significantly lower in NOAC group, especially rivaroxaban (coefficient 7.83, CI 4.44–11.22, p-value < 0.001) and dabigatran (coefficient 6.22, CI 2.67–9.77, p-value = 0.001) at 2 years.

**Conclusions:** Significant GFR decline was not uncommon in non-valvular AF patients who received anticoagulant. Among these, the proportion of patients who had significant eGFR decline (>30%) were comparable between NOACs and warfarin at 2 years. However, there is a significantly less mean eGFR decline per year in patients who receive NOACs, notably with dabigatran and rivaroxaban, than those who receive warfarin. The findings of this study should be interpreted in the context of patients included in this study.

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## 1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice but the management is challenging. The prevalence of AF was 1–4% in western countries [1–2] and 0.5–2% in other regions of the world [3]. Chronic kidney disease (CKD) was also a common comorbidity. Approximately one third of AF patients had CKD. They both shared common risk factors such as elderly, heart failure, hypertension and diabetes. In patients with AF and CKD, evidences suggested that there were higher risks of stroke, bleeding, and overall mortality [4–7].

Current evidences have clearly shown that vitamin K antagonists, mainly warfarin, reduced the risk of stroke and overall mortality when compared to placebo or aspirin [8]. However, recent data showed that some of patients who took warfarin had more

incidence of acute kidney injury (AKI) and worsening renal function, especially in patients with CKD in which this condition was defined as anticoagulant-related nephropathy [9–14]. The hypothesis of this phenomenon was that warfarin inhibited vitamin K dependent protein matrix gamma-carboxyglutamic acid and may facilitate renovascular calcification and, ultimately, led to the progression of CKD [12,15]. Furthermore, emerging evidences suggested that profuse glomerular hemorrhage was one of the major factors that contributed to acute kidney injury and possibly progressed to chronic kidney disease [16]. Glomerular hemorrhage with worsening of renal function as a result of excessive anticoagulation was initially reported in the literature in the early 2000s [17].

Non-vitamin K oral anticoagulants (NOACs) were increasingly prescribed because of their better profiles of stroke prevention and bleeding outcomes, and in particular, the reduced intracranial hemorrhage aspect when compared to warfarin [18]. Emerging data suggested that NOACs may be associated with slowing progression of CKD by inhibiting factor Xa and thrombin, which were associated with reduction of vascular inflammation [19–23]. Not all

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NOACs exhibited this favorable effects. The impact on renal function of these newer agents have not been extensively investigated especially in east asian ethnicity.

We aimed to study the 2-year renal outcomes in patients with atrial fibrillation who took oral anticoagulant for stroke prevention with either warfarin or NOACs (dabigatran, rivaroxaban, and apixaban).

## 2. Methods

### 2.1. Study population

This study was a retrospective cohort study using database from Phramongkutklao College of Medicine hospital. Non-valvular AF patients who took oral anticoagulants for at least 1 year were included in this study. The exclusion criteria were end-stage renal disease (ESRD) patients who received renal replacement therapy (RRT) or kidney transplantation and patients whom data of kidney function were missing. The protocol was reviewed and approved by the institutional ethics committee.

### 3. Study protocols

Data were collected from from 1st January 2011 to 31st July 2018. Baseline characteristics, continuation of oral anticoagulants, serum creatinine level and eGFR were reviewed from medical records and electronic database. Baseline characteristics included age, sex, DM, and CHA<sub>2</sub>DS<sub>2</sub>VAS score and any other underlying diseases were collected. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The adherence to NOACs and warfarin was also confirmed by the pill count protocol from the pharmacy department of the hospital. This protocol was compulsory for all medications which were reimbursed by the government. If the patients stopped all anticoagulants for >12 weeks or permanently, they were excluded from the analysis. The 12 -week period was the maximal allowance period for government reimbursement of medications on each visit. If the dose was reduced inadvertently or intentionally, they were still qualified in the analysis. All patients received standard dose and dose reduction according to guideline recommendations. For dabigatran, both 150 and 110 mg. were approved. The 75 mg of dabigatran was not approved in Thailand. For rivaroxaban, the standard dose was 20 mg. Rivaroxaban 15 mg. was used when eGFR was <50 ml/min. Rivaroxaban 10 mg was not approved in Thailand. For apixaban, the standard dose was 5 mg twice daily. The dose reduction would be required if 2 of 3 criteria were met that were 1) Cr > 1.5 mg/dL, 2) age > 80 years and 3) body weight < 60 kg.

### 4. Atrial fibrillation definition

The atrial fibrillation is defined according to 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation and as followed,

Electrocardiographic characteristics of AF include:

- Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired),
- Absence of distinct repeating P waves, and
- Irregular atrial activations.

### 5. Renal outcomes

We evaluated 3 primary renal outcomes: Significant eGFR decline (defined as > 30% decline in GFR), doubling of serum creatinine, and kidney failure requiring RRT at 2 years as primary study

outcomes. Significant GFR decline was defined in accordance with the US National Kidney Foundation and Food Drug Administration (FDA) that concluded that 30% decline in GFR over 2–3 years was a reasonable surrogate endpoint in clinical research [24]. All patients were required to have eGFR at baseline, 1 year and 2 years after starting oral anticoagulants for the analysis of primary outcomes. For patients with eGFR decline <30%, eGFR decline > 10–20%, eGFR decline > 20–30% and mean eGFR decline per year were also included as the secondary study outcomes. Patients who completed oral anticoagulants for 2 years were analyzed for the primary outcomes whereas those who took at least 1 year of oral anticoagulants were eligible for secondary outcomes. The frequency of eGFR reading per year in our institute were in parallel with the 2018 EHRA non vitaminK antagonist guidelines [25], stated that the minimum interval of eGFR monitor is the eGFR/10. Stage of GFR were defined as followed, stage 1 (eGFR > 90 ml/min/1.73 m<sup>2</sup>), stage 2 (eGFR 60–90 ml/min/1.73 m<sup>2</sup>), stage 3 (eGFR 30–59 ml/min/1.73 m<sup>2</sup>), stage 4 (eGFR 15–29 ml/min/1.73 m<sup>2</sup>) and stage 5 (eGFR < 15 ml/min/1.73 m<sup>2</sup>).

### 6. Sample size calculations

Previous study from Xiaoxi Yao, et al [23] found that patients who took Rivaroxaban and Dabigatran were associated with significant lower of GFR decline when compared with warfarin, with hazard ratio of 0.73 (95 %CI 0.56–0.95 for Dabigatran and 0.61–0.86 for Rivaroxaban). Sample size was calculated using 80% power to show significant GFR decline at alpha level of 0.05. Total sample size was 317 patients in each group.

### 7. Statistical analysis

Descriptive statistics were used to show baseline characteristics. Event rate, plotted Kaplan-Meier Curves and estimated the cumulative risks at 12 and 24 months were calculated. Chi-square test and Fisher's exact test were used to compare the significant GFR decline in warfarin group and NOACs group. Independent *t*-test and Mann-Whitney *U* test were used to compare the rate of GFR decline per year. The Cox proportional hazards regression model was used for the adjusted hazard ratio to compare the significant GFR decline in warfarin group and NOACs group. Multiple linear regression analysis was used to compare the mean GFR change in warfarin group and NOACs group.

### 8. Subgroup analysis

Subgroup analysis were performed by using the following parameters; diabetes mellitus, presence of CKD at baseline (GFR < 60%), and stroke risk stratified by CHA<sub>2</sub>DS<sub>2</sub>VASc score (Low risk as score 0–1, Intermediate risk as score 2–3, High risk as score at least 4).

### 9. Results

#### 9.1. Baseline characteristics

We identified 734 patients with non-valvular AF who received oral anticoagulants for stroke prevention which consisted of 320 patients in warfarin group and 414 patients in NOACs group (144 patients in Dabigatran group, 199 patients in Rivaroxaban group and 71 patients in Apixaban group). All patients in warfarin group completed the 2-year follow up period, but 289 patients of 414 patients in NOACs group were eligible for 2-year follow up period analysis (Fig. 1). Baseline characteristics of patients were demonstrated (Table 1). Most of baseline characteristics were balanced

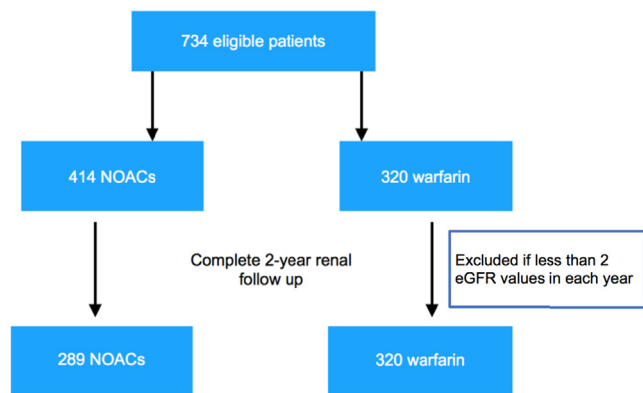


Fig. 1. Flow chart of eligible patients.

Table 1  
Baseline Characteristics of patients with NOAC and warfarin.

|                                | NOAC (n = 414)<br>n(%) | Warfarin (n = 320)<br>n(%) | p-value |
|--------------------------------|------------------------|----------------------------|---------|
| <b>Age (yrs)</b>               |                        |                            | 0.612‡  |
| Mean ± SD                      | 71.48 ± 10.34          | 71.86 ± 9.24               |         |
| <b>Sex</b>                     |                        |                            | 0.624   |
| Male                           | 254 (61.35)            | 202 (63.13)                |         |
| Female                         | 160 (38.65)            | 118 (36.88)                |         |
| <b>Valvular Heart Disease</b>  | 1 (2.94)               | –                          | 0.096†  |
| <b>Stroke</b>                  | 134 (32.37)            | 81 (25.31)                 | 0.037   |
| <b>Heart failure</b>           | 52 (12.56)             | 39 (12.19)                 | 0.879   |
| <b>Hypertension</b>            | 289 (69.81)            | 249 (77.81)                | 0.015   |
| <b>Diabetes</b>                | 114 (27.54)            | 93 (29.06)                 | 0.649   |
| <b>Coronary artery disease</b> | 61 (14.73)             | 52 (16.25)                 | 0.573   |
| <b>Use of Antiplatelet</b>     | 60 (14.49)             | 55 (17.19)                 | 0.319   |
| <b>CHA2DS2VASc score</b>       |                        |                            | 0.971¥  |
| Mean ± SD                      | 3.42 ± 1.67            | 3.41 ± 1.4                 |         |
| <b>Baseline Cr</b>             |                        |                            | 0.811‡  |
| Mean ± SD                      | 1.07 ± 0.29            | 1.08 ± 0.35                |         |
| <b>Baseline GFR</b>            |                        |                            | 0.443‡  |
| Mean ± SD                      | 65.94 ± 17.47          | 66.96 ± 18.66              |         |

NOAC = Non vitaminK Oral anticoagulant, eGFR = Glomerular filtration rate (ml/min/1.73 m<sup>2</sup>)

† Fisher's exact test,

‡ Independent t-test,

¥ Mann-Whitney U test, Significant if p < 0.05.

between two groups except for hypertension which was more common in warfarin group and history of stroke which was more common in NOACs group.

### 10. Renal outcomes

There were 3 primary renal outcomes as mentioned above at the end of 2-year follow up. None of the patients in this study had doubling serum creatinine nor kidney failure requiring renal replacement therapy. The number of patients with significant GFR decline were 28 patients (9.69%) in NOACs group and 35 patients (10.94%) in warfarin group. The incidence rate of significant eGFR decline (eGFR drop > 30%) were comparable in NOACs and warfarin group which were 4.82 and 5.38 (HR 1.01 CI 0.62–1.66, p-value 0.964) respectively. This HR remained nonsignificant even when adjusted for baseline characteristics (HR 1.12 CI 0.67–1.87, p-value 0.678) and CHA2DS2VASc score (HR 0.97 CI 0.59–1.59, p-value 0.891) as demonstrated (Table 2). The cumulative risk of significant GFR drop > 30% between NOACs and warfarin group (Fig. 2A) was also indifferent (p-value 0.632) at 2 years. There was also no significant difference in the cumulative risk of significant GFR drop > 30% between different NOACs and warfarin (p-value

0.092)(Fig. 2 B). The higher proportion of patients with > 30% eGFR drop at 1 year was observed in patients who received apixaban when compared with warfarin. However, this proportion seemed to be comparable with warfarin at 2 years (Fig. 3).

The subgroup analysis using the following parameters; diabetes mellitus, presence of CKD at baseline (GFR<60%) and stroke risk stratified by CHA2DS2VASc score (Low risk as score 0–1, Intermediate risk as score 2–3, High risk as score at least 4), there were no significant interactions within subgroup between patients who received warfarin and NOACs (Table 3).

In secondary renal analysis of mean GFR change per year (for patients with GFR declined < 30%), when adjusted for several baseline characteristics and CHA2DS2VASc score, the adjusted mean eGFR change remained significantly lower in patients who received NOAC at 1 year and 2 years as presented by Coefficient or β (Table 4A–4B). When adjusted for baseline characteristics, dabigatran had 3.96 ml/min/1.73 m<sup>2</sup> lower of adjusted mean eGFR change per year, in comparison with warfarin, at 1 year (CI 1.07–6.86, p-value 0.007) and 5.78 ml/min/1.73 m<sup>2</sup> lower of adjusted mean eGFR change per year at 2 years (CI 2.23–9.33, p-value 0.001). Rivaroxaban had 3.85 ml/min/1.73 m<sup>2</sup> lower of adjusted mean eGFR change per year, in comparison with warfarin, at 1 year (CI 1.31–6.4, p-value 0.003) and 7.03 ml/min/1.73 m<sup>2</sup> lower of adjusted mean eGFR change per year at 2 years (CI 3.66–10.4, p-value < 0.001). The same direction of change was also observed for both dabigatran and rivaroxaban when adjusted for CHA2DS2VASc score. Treatment with apixaban conferred approximately the same mean GFR change per year as with warfarin even when adjusted for baseline characteristics and CHA2DS2VASc score.

The proportion of patients with 10–20% of eGFR drop at 1 year and 2 years were demonstrated in Fig. 4A–4B. There were lower proportion of patients with 10–20% eGFR drop in those who received NOACs than in warfarin group, especially with rivaroxaban (34.75% vs. 57.81%, p-value < 0.001) and dabigatran (41.94% vs. 57.81%, p-value = 0.003) at 2 years. Likewise, the proportion of patients with 20–30% of eGFR drop at 1 year and 2 years were demonstrated in Fig. 5A–5B. Patients who received rivaroxaban were consistently less likely to develop the decline of 20–30% of eGFR, when compared with warfarin at 2 years (17.73% vs. 26.88%, p-value 0.02 and p-value 0.034 respectively).

### 11. Discussion

We clearly demonstrated that significant GFR decline is not uncommon among these groups of patients. Our data revealed that the rate of significant GFR decline are comparable in both groups at 2-year follow up. The incidence rate of significant GFR decline is 4.82 and 5.38 per 100 person-year in NOACs and warfarin group respectively, without significant difference between the two groups. Our findings report the lower incidence rate of renal outcomes when compared to previous study [23]). Co-morbidities that may have significant effects on eGFR decline such as heart failure, diabetes and hypertension are also numerically lower, for example, our study includes about 27–29% of diabetes patients in both groups. However, we do not observe any significant difference in significant eGFR decline between NOAC and warfarin from our diabetes subgroup analysis. Although the time course of 2–3 years are the acceptable surrogate renal endpoints [24], the worsening renal function can occur at any time course during treatment with anticoagulants and appropriate anticoagulant dosage adjustment must be implemented promptly. The rate of GFR decline per year is not negligible and there is quite limited data reported on this change so we incorporate this short term change of eGFR in our analysis. NOACs is associated with significantly less mean eGFR decline per year when compared with warfarin especially dabigatran and

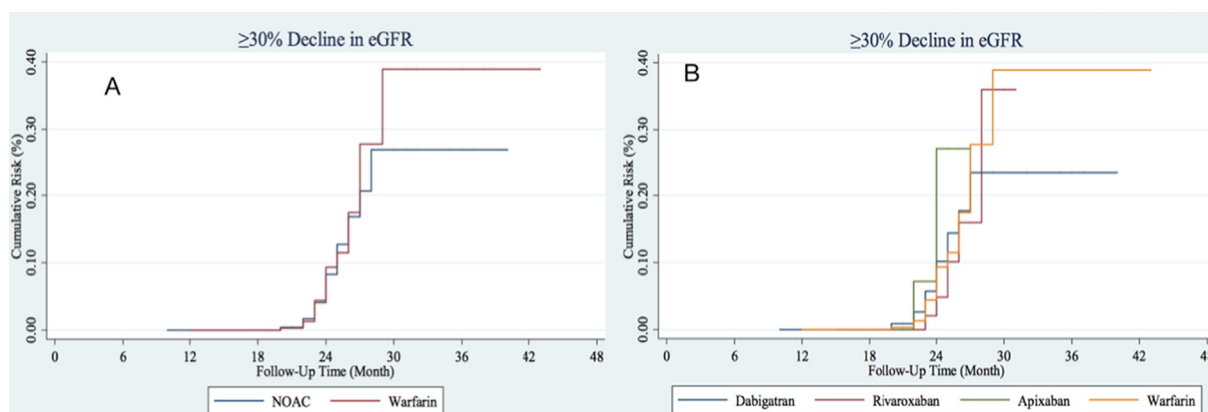
**Table 2**  
Adjusted hazard ratio of significant GFR drop > 30% in NOACs and warfarin group at 2 years.

| Drug                 | Total | GFR drop > 30% | Exposure time | Incidence rate  | HR (95 %CI)      | p-value | HR (95 %CI)*                          | p-value | HR (95 %CI)**            | p-value |
|----------------------|-------|----------------|---------------|-----------------|------------------|---------|---------------------------------------|---------|--------------------------|---------|
|                      | n(%)  | n(%)           | (year)        | 100 person year |                  |         | Adjusted for Baseline Characteristics |         | Adjusted for CHA2DS2VASc |         |
| NOAC                 | 289   | 28 (9.69)      | 581.42        | 4.82            | 1.01 (0.62–1.66) | 0.964   | 1.12 (0.67–1.87)                      | 0.678   | 0.97 (0.59–1.59)         | 0.891   |
| Warfarin             | 320   | 35 (10.94)     | 650.42        | 5.38            | Reference        |         | Reference                             |         | Reference                |         |
| <b>Drug subgroup</b> |       |                |               |                 |                  |         |                                       |         |                          |         |
| Dabigatran           | 124   | 13 (10.48)     | 252.25        | 5.15            | 0.98 (0.52–1.87) | 0.960   | 1.05 (0.54–2.02)                      | 0.897   | 0.95 (0.50–1.81)         | 0.879   |
| Rivaroxaban          | 141   | 11 (7.80)      | 283.50        | 3.88            | 0.85 (0.43–1.67) | 0.627   | 0.99 (0.50–1.98)                      | 0.982   | 0.93 (0.47–1.85)         | 0.844   |
| Apixaban             | 24    | 4 (16.67)      | 45.67         | 8.76            | 2.75 (0.98–7.76) | 0.056   | 2.60 (0.89–7.58)                      | 0.080   | 2.48 (0.86–7.17)         | 0.094   |
| Warfarin             | 320   | 35 (10.94)     | 650.42        | 5.38            | Reference        |         | Reference                             |         | Reference                |         |

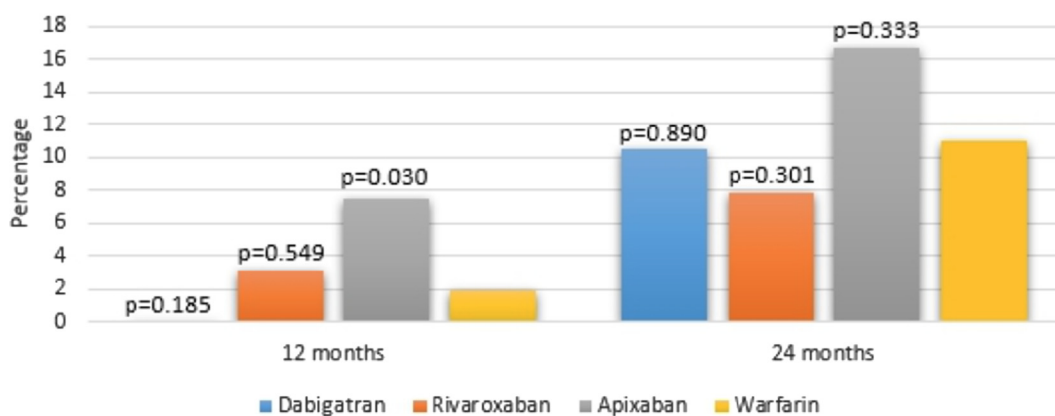
Cox proportional hazards regression models analysis, Significant if p < 0.05.  
NOAC = Non vitaminK Oral anticoagulant, eGFR = Glomerular filtration rate(ml/min/1.73 m2).

\* Adjusted for age, sex, stroke, Diabetes.

\*\* Adjusted for CHA2 DS2 VASc.



**Fig. 2.** Cumulative risk of significant GFR drop > 30% between NOAC and warfarin (2A) and between individual NOAC and warfarin(2B) at 2 years, A. Log-rank test between warfarin and NOAC at 24 months . p = 0.632, B. Log-rank test between 3 NOAC drugs and warfarin at 24 months . p = 0.092, NOAC = Non vitaminK Oral anticoagulant , eGFR = Glomerular filtration rate(ml/min/1.73 m2), Significant if p < 0.05.



**Fig. 3.** The proportion of patients with > 30% eGFR drop at 1 year and 2 years in comparison with warfarin, Unadjusted for other covariates. All NOACs were compared with warfarin . Significant if p < 0.05, NOAC = Non vitaminK Oral anticoagulant , eGFR = Glomerular filtration rate(ml/min/1.73 m2).

rivaroxaban. Apixaban demonstrates comparable mean eGFR change per year with warfarin. The initial report of acute kidney injury after NOAC introduction revealed the glomerular bleeding which resulted in red blood cell casts obstruction, aggravated pre-existing kidney injury and resulted in worsening kidney function [16]. Yao et al. also demonstrated the favorable renal outcomes in patients who received rivaroxaban and dabigatran but not apix-

aban when compared with warfarin[23]. From our results, we could not definitely confirm whether warfarin caused worsening renal function or NOACs had favorably preserved kidney function. We observe approximately 3–6 ml/min/1.73 m<sup>2</sup> lower of mean eGFR change per year in patients who receive NOACs at 1 and 2 years. Brodsky et al. suggested that patients who took warfarin and experienced INR > 3 were more likely to develop nephropathy

**Table 3**  
Subgroup analysis of patients with significant eGFR drop > 30% in NOACs and warfarin group.

|                        | Warfarin | NOAC   | HR    | 95 %CI<br>Lower | Upper | p-value |
|------------------------|----------|--------|-------|-----------------|-------|---------|
| <b>CKD at baseline</b> |          |        |       |                 |       |         |
| GFR ≥ 60               | 19/198   | 18/180 | 1.120 | 0.586           | 2.140 | 0.731   |
| GFR < 60               | 16/122   | 10/109 | 0.875 | 0.395           | 1.936 | 0.742   |
| <b>DM</b>              |          |        |       |                 |       |         |
| Non-DM                 | 23/227   | 13/216 | 0.675 | 0.342           | 1.333 | 0.257   |
| DM                     | 12/93    | 15/73  | 1.908 | 0.889           | 4.081 | 0.098   |
| <b>CHADVAS Score</b>   |          |        |       |                 |       |         |
| Low (0–1)              | 3/24     | 1/36   | 0.218 | 0.022           | 2.112 | 0.189   |
| Moderate (2–3)         | 9/154    | 13/111 | 2.188 | 0.934           | 5.126 | 0.072   |
| High (≥4)              | 23/142   | 14/142 | 0.771 | 0.396           | 1.501 | 0.445   |

The unadjusted hazard ratio of patients with significant eGFR drop > 30% who received warfarin versus NOACs according to eGFR, DM and CHA2DS2VASc status.  
DM = Diabetes Mellitus , CKD = chronic kidney disease , NOAC = Non vitaminK Oral anticoagulant, Significant if p < 0.05.

**Table 4**  
The adjusted mean eGFR change per year of NOACs and warfarin at 1 year(4A) and 2 years(4B).

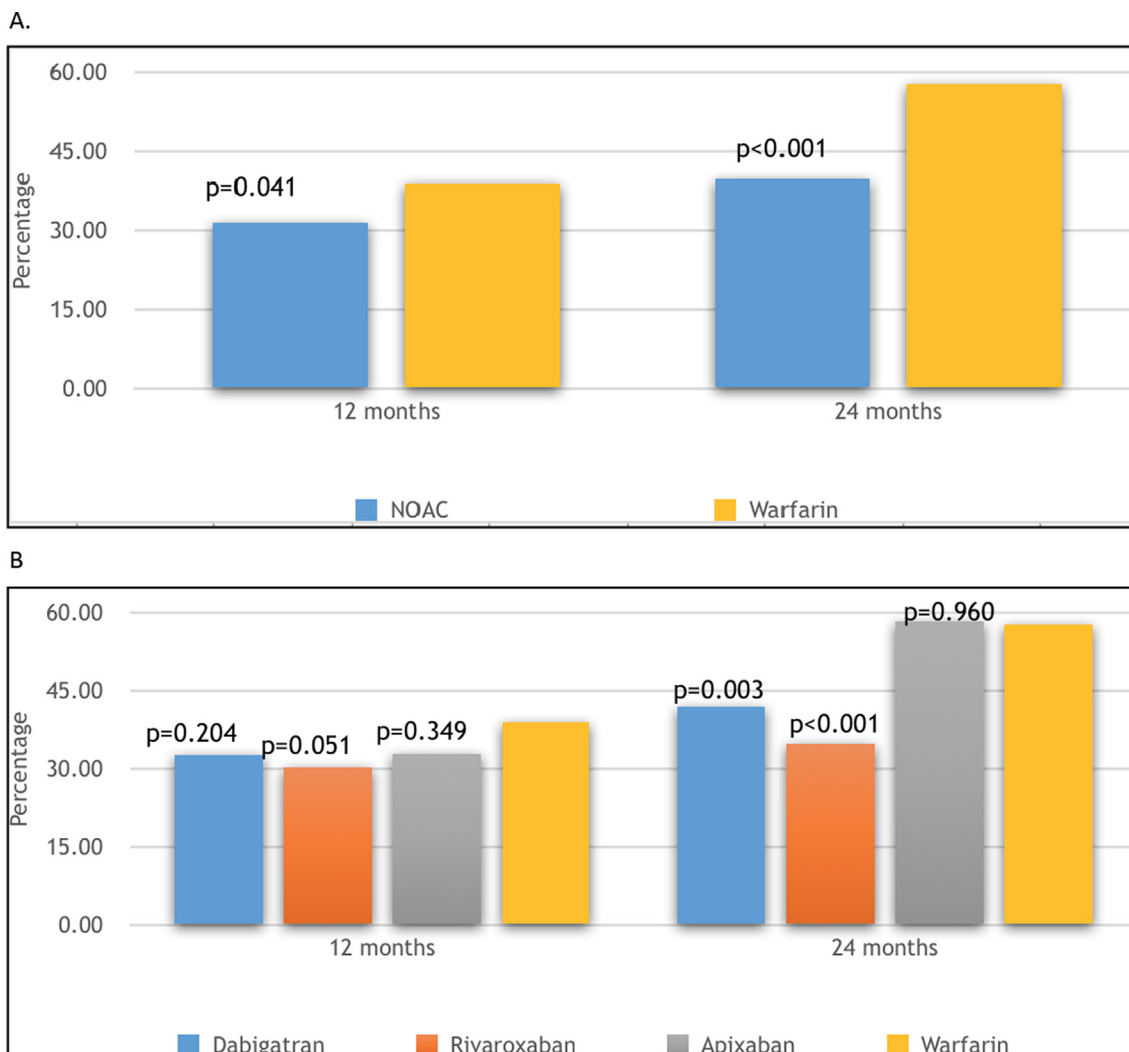
| A             |     |                 |                     |                      |                                       |                       |                          |                        |         |
|---------------|-----|-----------------|---------------------|----------------------|---------------------------------------|-----------------------|--------------------------|------------------------|---------|
| Drug          | n   | Baseline<br>GFR | Mean GFR<br>at 1-yr | Coefficient (95 %CI) | p-value                               | Coefficient (95 %CI)* | p-value                  | Coefficient (95 %CI)** | p-value |
|               |     |                 |                     |                      | Adjusted for Baseline Characteristics |                       | Adjusted for CHA2DS2VASc |                        |         |
| Drug          |     |                 |                     |                      |                                       |                       |                          |                        |         |
| NOAC          | 390 | 65.75 ± 17.35   | 63.09 ± 17.54       | 3.97 (1.86–6.09)     | <0.001                                | 3.5 (1.39–5.6)        | 0.001                    | 3.7 (1.6–5.8)          | 0.001   |
| Warfarin      | 308 | 67.21 ± 18.77   | 62.22 ± 18.67       | Reference            |                                       | Reference             |                          | Reference              |         |
| Drug subgroup |     |                 |                     |                      |                                       |                       |                          |                        |         |
| Dabigatran    | 132 | 66.46 ± 16.59   | 63.99 ± 16.05       | 4.42 (1.54–7.3)      | 0.003                                 | 3.96 (1.07–6.86)      | 0.007                    | 4.38 (1.52–7.24)       | 0.003   |
| Rivaroxaban   | 191 | 67.44 ± 16.91   | 64.84 ± 17.3        | 4.14 (1.59–6.7)      | 0.002                                 | 3.85 (1.31–6.4)       | 0.003                    | 3.9 (1.35–6.45)        | 0.003   |
| Apixaban      | 67  | 59.57 ± 18.87   | 56.34 ± 19.61       | 2.61 (-1.12–6.35)    | 0.170                                 | 1.56 (-2.19–5.31)     | 0.415                    | 1.77 (-1.97–5.52)      | 0.352   |
| Warfarin      | 308 | 67.21 ± 18.77   | 62.22 ± 18.67       | Reference            |                                       | Reference             |                          | Reference              |         |
| B             |     |                 |                     |                      |                                       |                       |                          |                        |         |
| Drug          | n   | Baseline<br>GFR | Mean GFR<br>at 2-yr | Coefficient (95%CI)  | p-value                               | Coefficient (95%CI)*  | p-value                  | Coefficient (95%CI)**  | p-value |
|               |     |                 |                     |                      | Adjusted for Baseline Characteristics |                       | Adjusted for CHADVAS     |                        |         |
| Drug          |     |                 |                     |                      |                                       |                       |                          |                        |         |
| NOAC          | 289 | 66.22 ± 17.33   | 61.59 ± 18.41       | 6.67 (3.94–9.39)     | <0.001                                | 5.96 (3.23–8.68)      | 0.001                    | 6.35 (3.64–9.05)       | <0.001  |
| Warfarin      | 320 | 66.96 ± 18.66   | 58.62 ± 18.58       | Reference            |                                       | Reference             |                          | Reference              |         |
| Drug subgroup |     |                 |                     |                      |                                       |                       |                          |                        |         |
| Dabigatran    | 124 | 66.49 ± 17.37   | 61.49 ± 18.43       | 6.22 (2.67–9.77)     | 0.001                                 | 5.78 (2.23–9.33)      | 0.001                    | 6.28 (2.76–9.8)        | <0.001  |
| Rivaroxaban   | 141 | 67.78 ± 16.89   | 63.86 ± 18.08       | 7.83 (4.44–11.22)    | <0.001                                | 7.03 (3.66–10.4)      | <0.001                   | 7.35 (3.96–10.74)      | <0.001  |
| Apixaban      | 24  | 55.68 ± 16.70   | 48.87 ± 15.34       | 2.14 (-4.97–9.24)    | 0.555                                 | 0.38 (-6.71–7.47)     | 0.917                    | 0.73 (-6.38–7.83)      | 0.841   |
| Warfarin      | 320 | 66.96 ± 18.66   | 58.62 ± 18.58       | Reference            |                                       | Reference             |                          | Reference              |         |

Multiple linear regression analysis, Significant if p < 0.05.  
Coefficient or β for mean eGFR = ml/min/1.73 m2.  
NOAC = Non vitaminK Oral anticoagulant, eGFR = Glomerular filtration rate(ml/min/1.73 m2).  
\* Adjusted for baseline characteristics which were age, sex, stroke, diabetes, baseline eGFR and baseline creatinine.  
\*\* Adjusted for CHA2 DS2 VASc score.

and the second factor was also required such as reduced number of nephrons or acute damage to the glomeruli by excessive bleeding [16]. Furthermore, the same mechanism was extensively reported in warfarin and it also accounted for worsening renal function in patients who received other forms of vitaminK antagonist molecules[14]. This might support the notion that warfarin caused worsening renal function through several mechanisms rather than the novel profile on kidney function of NOACs. This conclusion might need a further large-scale study to draw the final conclusion. Maintaining stable renal function after treatment with oral anticoagulants is a cornerstone of treatment because worsening of renal function is associated with increased risks of both ischemic events and bleeding complication and subsequently affects the clinical outcomes. When choosing anticoagulant for stroke prevention, the impact of drug on renal function may need to be considered.

The strength of our study were as followed. First, we also analyzed the rate of significant GFR decline according to CHA2DS2VASc

score. Although we do not observe any significant impact of low CHA2DS2VASc score (0–1), intermediate CHA2DS2VASc score (2–3) and high CHA2DS2VASc score (>4) on significant GFR decline at 2 years but we do observe a high proportion of patients with eGFR decline over time in patients with high CHA2DS2VASc who received warfarin and NOACs at 2 years accordingly. This data highlight the importance of meticulous GFR measurement and potentially more frequent GFR measurement in those patients with preexisting high CHA2DS2VASc score because this may have the significant impact on subsequent dosage modification of NOACs and other medications that might be affected by declining eGFR. Furthermore, a thorough search of possible causes of GFR decline should always be investigated. Second, we are among the few publications that report the eGFR decline at lower degree, from > 10–20% to > 20–30% of eGFR decline. This highlights the fact that NOACs ,especially dabigatran and rivaroxaban, has favorable renal effects even with mild degree of GFR decline when compared with warfarin. Third, we can demonstrate in detail the mean change of



**Fig. 4.** The proportion of patients with > 10–20% eGFR drop at 1 year and 2 years between NOAC and warfarin (4A) and between individual NOAC and warfarin(4B). Unadjusted for other covariates. All NOACs were compared with warfarin . Significant if  $p < 0.05$ , NOAC = Non vitaminK Oral anticoagulant , eGFR = Glomerular filtration rate (ml/min/1.73 m<sup>2</sup>).

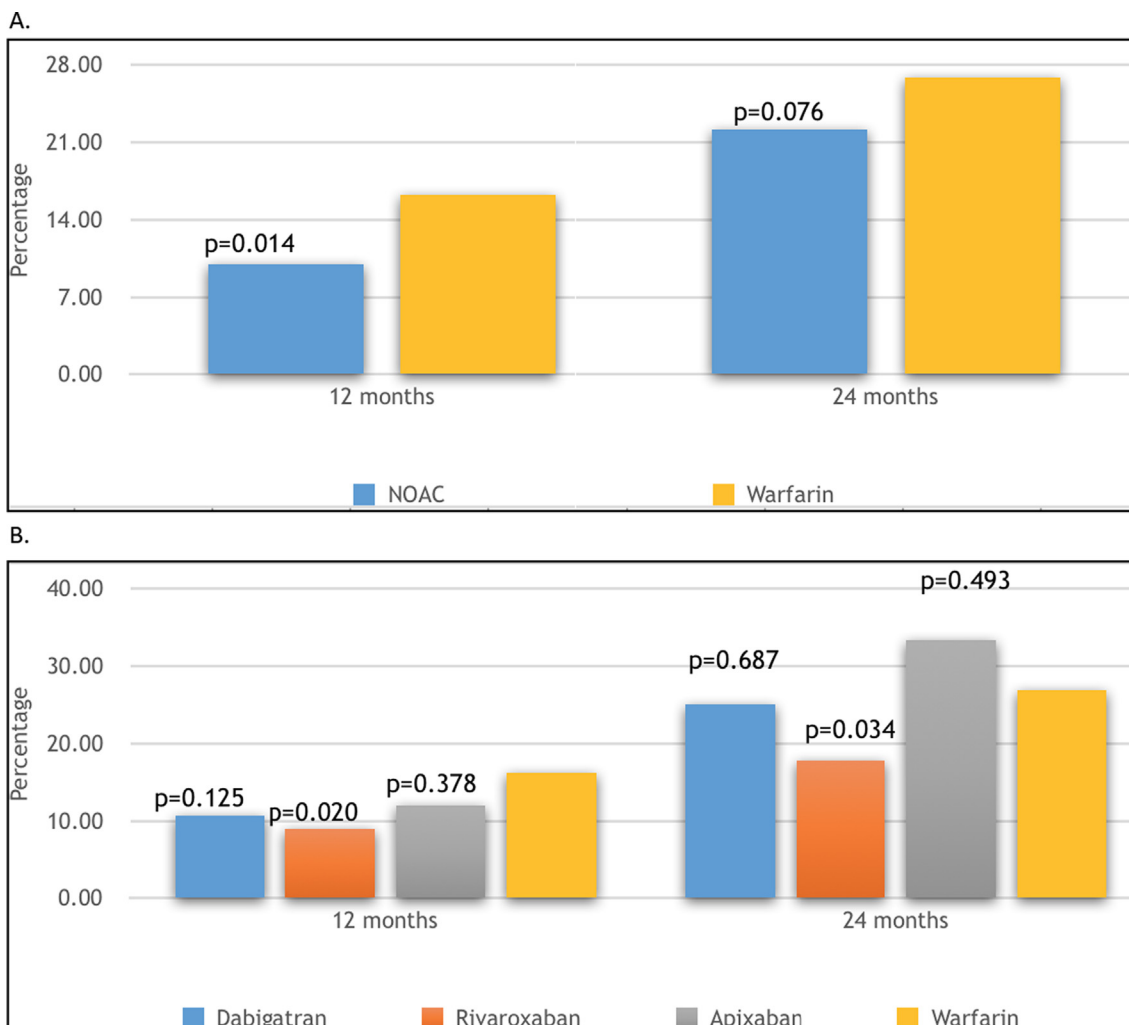
eGFR per year in patients who receive different types of NOACs and warfarin as mentioned earlier. Lastly, the eGFR were uniformly calculated by EPI formula at our institute which made the data more consistent on the method of eGFR calculation. Several previous reports use claimed-based data which the detail of eGFR calculation may be missing and may potentially be confounded by different methods of eGFR calculation when they are combined the pool eGFR data analysis.

This study had also some limitations. First, this study was a retrospective study. There may be several residual uncontrolled confounders in the analysis. There were also high rate of drop out at 2-year follow up in NOACs group. Although all patients will be asked about medication adherence but it was also impossible to confirm the true adherence to NOACs. For warfarin, adherence can be monitored through the INR but, again, the below range INR does not necessarily mean the poor compliance to warfarin. However, none of the patient had skipped the refill of prescription for >3 months since they will be excluded from the analysis. Second, since apixaban was available in our institute in the year 2015, the numbers of apixaban patients constituted a small proportion of patients in NOACs group who completed 2 years renal follow-up. The assumption that apixaban has less favorable renal profile required further large scale study. Third, All patients

received standard dose and reduced dose according to guideline recommendations[25]. All patients received initial standard dose and the majority of patients remained at standard dose until the end of 2-year follow up. However, all of dabigatran patients received only 110 mg-dose because this is the only dose that is available in the the pharmacy department in our hospital. Unfortunately, we are unable to analyze the proportion of patients that subsequently receive the reduced dose for rivaroxaban and apixaban. Some of these patients had dose reduction at different duration, ranging from a few weeks to a few months before the end of the 2-year analysis. However, these patients constituted <5 percents of the total patients. Fourth, we did not perform the subgroup analysis of significant GFR decline according to stage of CKD and presence or absence of coronary artery disease because of the small number of subjects. Lastly, we did not report TTR and dosage of warfarin used in our study because warfarin dosage were frequently adjusted as per physicians discretion.

**12. Conclusion**

Significant GFR decline was not uncommon in non-valvular AF patients who received anticoagulant. Among these, the proportion of patients who had significant eGFR decline(>30%) were compara-



**Fig. 5.** The proportion of patients with > 20–30% eGFR drop at 1 year and 2 years between NOAC and warfarin (5A) and between individual NOAC and warfarin(5B), Unadjusted for other covariates. All NOACs were compared with warfarin . Significant if  $p < 0.05$ , NOAC = Non vitaminK Oral anticoagulant , eGFR = Glomerular filtration rate (ml/min/1.73 m<sup>2</sup>).

ble between NOACs and warfarin at 2 years. However, there is a significantly less mean eGFR decline per year in patients who receive NOACs, notably with dabigatran and rivaroxaban, than those who receive warfarin. However, the findings of this study should be interpreted in the context of patients included in this study and may not be generalizable.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**References**

[1] F. Rahman, G.F. Kwan, E.J. Benjamin, Global epidemiology of atrial fibrillation, *Nat Rev Cardio* 11 (2014) 639–654.  
 [2] L. Friberg, L. Bergfeldt, Atrial fibrillation prevalence revisited, *J Intern Med* 274 (2013) 461–468.

[3] C.X. Wong, A. Brown, C.M. Albert, et al., Epidemiology of atrial fibrillation: The Australian and Asia-Pacific perspective, *Heart Lung Circ* 26 (2017) 870–879.  
 [4] Y.C. Lau, M. Proietti, E. Guiducci, et al., Atrial fibrillation and thromboembolism in patients with chronic kidney disease, *J Am Coll Cardiol* 68 (2016) 1452–1464.  
 [5] N. Kulkarni, N. Gukathasan, S. Sartori, Chronic kidney disease and atrial fibrillation: A contemporary overview, *J Afib* 5 (2012) 62–70.  
 [6] T.F. Chao, S.A. Chen, Risk of ischemic stroke and stroke prevention in patients with atrial fibrillation and renal dysfunction, *J Afib* 8 (2015) 62–67.  
 [7] W.T. Zeng, X.T. Sun, K. Tang, et al., Risk of thromboembolic events in atrial fibrillation with chronic kidney disease, *Stroke* 46 (2015) 157–163.  
 [8] R.G. Hart, L.A. Pearce, M.I. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, *Ann Intern Med* 146 (2007) 857–867.  
 [9] V.B. Sergey, N. Tibor, H.R. Brad, et al., Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate, *Kidney International* 80 (2011) 181–189.  
 [10] D.S. Wheeler, R.P. Giugliano, J. Rangaswami, Anticoagulation-related nephropathy, *J Thromb Haemost* 14 (2016) 461–467.  
 [11] N.K. Vinay, G.W. David, S. Nakshatra, et al., Oral Anticoagulants and Risk of Nephropathy, *Drug Saf* 38 (2015) 527–533.  
 [12] M.L. Chatrou, K. Winkers, T.M. Hackeng, C.P. Reutelingsperger, L.J. Schurgers, Vascular calcification: the price to pay for anticoagulation therapy with vitamin K-antagonists, *Blood Rev* 26 (2012) 155–166.  
 [13] Sergey Brodsky, John Eikelboom, Lee A. Hebert, et al., Anticoagulant-Related Nephropathy, *J Am Soc Nephrol* 29 (2018) 2787–2793.  
 [14] Leonard Golbin, Cecile Vigneau, Guy Touchard, Eric Thervet, et al., Warfarin-related nephropathy induced by three different vitamin K antagonists: analysis of 13 biopsy-proven cases, *Clinical Kidney Journal* 10 (3) (2017) 381–388.

- [15] L.J. Schurgers, I.A. Joosen, E.M. Laufer, et al., Vitamin K-antagonists accelerate atherosclerotic calcification and induce a vulnerable plaque phenotype, *PLoS One* 7 (2012) e43229.
- [16] S.V. Brodsky, N.S. Mhaskar, S. Thiruveedi, R. Dhingra, S.C. Reuben, E. Calomeni, et al., Acute kidney injury aggravated by treatment initiation with apixaban: Another twist of anticoagulant-related nephropathy, *Kidney Res Clin Pract* 36 (2017) 387–392.
- [17] A.B. Abt, L.E. Carroll, J.H. Mohler, Thin basement membrane disease and acute renal failure secondary to gross hematuria and tubular necrosis, *Am J Kidney Dis* 35 (2000) 533–536.
- [18] C.T. Ruff, R.P. Giugliano, E. Braunwald, et al., Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials, *Lancet* 383 (2014) 955–962.
- [19] B. Michael, D.E. Michael, J.C. Stuart, et al., Changes in Renal Function in Patients With Atrial Fibrillation - An Analysis from the RE-LY Trial, *J Am Coll Cardiol* 65 (2015) 2481–2493.
- [20] C. Yi-Hsin, Y. Yung-Hsin, S. Lai-Chu, et al., Acute Kidney Injury in Asians With Atrial Fibrillation Treated with Dabigatran or Warfarin, *J Am Coll Cardiol* 68 (2016) 2272–2283.
- [21] H. Ziad, H.H. Stefan, A. Ulrika, et al., Efficacy and Safety of Apixaban Compared with Warfarin in Patients with Atrial Fibrillation in Relation to Renal Function Over Time - Insights from the ARISTOTLE Randomized Clinical Trial, *JAMA Cardiol.* 1 (4) (2016) 451–460.
- [22] B.F. Christopher, S.H. Anne, L. Yuliya, et al., On-treatment Outcomes in Patients With Worsening Renal Function with Rivaroxaban compared with Warfarin - Insights From ROCKET AF, *Circulation* 134 (2016) 37–47.
- [23] Y. Xiaoxi, T. Navdeep, J.G. Bernard, et al., Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation, *J Am Coll Cardiol* 70 (2017) 2621–2632.
- [24] Andrew SL, Lesley AI, Kunihiro M, et al. GFR Decline as an End Point for Clinical Trials in CKD. *Am J Kidney Dis.*64(6):821-835
- [25] J. Steffel, P. Verhamme, T.S. Potpara, et al., The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, *Eur Heart J* 00 (2018) 1–64.