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SYSTEMATIC REVIEW AND META-ANALYSIS

Non-Vitamin K Antagonist Oral Anticoagulants Provide Less Adverse Renal Outcomes Than Warfarin In Non-Valvular Atrial Fibrillation: A Systematic Review and MetaAnalysis

Patita Sitticharoenchai, MD; Kullaya Takkavatakarn, MD; Smonporn Boonyaratavej, MD; Kearkiat Praditpornsilpa, MD; Somchai Eiam-Ong, MD; Paweena Susantitaphong, MD, PhD

BACKGROUND: Non-vitamin K antagonist oral anticoagulants (NOACs) have better pharmacologic properties than warfarin and are recommended in preference to warfarin in most patients with non-valvular atrial fibrillation. Besides lower bleeding complications, other advantages of NOACs over warfarin particularly renal outcomes remain inconclusive.

METHODS AND RESULTS: Electronic searches were conducted through Medline, Scopus, Cochrane Library databases, and ClinicalTrial.gov. Randomized controlled trials and observational cohort studies reporting incidence rates and hazard ratio (HR) of renal outcomes (including acute kidney injury, worsening renal function, doubling serum creatinine, and end-stage renal disease) were selected. The random-effects model was used to calculate pooled incidence and HR with 95% CI. Eighteen studies were included. A total of 285 201 patients were enrolled, 118 863 patients with warfarin and 166 338 patients with NOACs. The NOACs group yielded lower incidence rates of all renal outcomes when compared with the warfarin group. Patients treated with NOACs showed significantly lower HR of risk of acute kidney injury (HR, 0.70, 95% CI, 0.64–0.76; $P<0.001$), worsening renal function (HR, 0.83; 95% CI, 0.73–0.95; $P=0.006$), doubling serum creatinine (HR, 0.58; 95% CI, 0.41–0.82; $P=0.002$), and end-stage renal disease (HR, 0.82; 95% CI, 0.78–0.86; $P<0.001$).

CONCLUSIONS: In non-valvular atrial fibrillation, patients treated with NOACs have a lower risk of both acute kidney injury and end-stage renal disease when compared with warfarin.

Key Words: acute kidney injury ■ end-stage renal disease ■ NOACs ■ non-valvular atrial fibrillation ■ renal outcomes ■ warfarin

Atrial fibrillation (AF) is one of the most common types of cardiac arrhythmia.[1] The prevalence of AF has been increasing worldwide, particularly in the aging population and in patients with chronic kidney disease (CKD).[2,3] When AF occurs, the blood clots can be easily formed in the atria, and this can cause cardiac embolism. Accordingly, prevention therapy of cardiac embolism, especially ischemic stroke, with oral anticoagulant, is the cornerstone in AF management in the general population and patients with CKD.[4]

Nowadays, oral anticoagulants are recommended in patients with AF with high CHA_2DS_2VASc score.[4,5] In selection of anticoagulant medication, the following issues should be considered: side effects, drug interactions, patient comorbidities, and patient compliance. Heretofore, warfarin, a vitamin K antagonist,

Correspondence to: Paweena Susantitaphong, MD, PhD, Division of Nephrology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, 1873 RAMA IV, Bangkok 10330, Thailand. E-mail: pesancerinus@hotmail.com

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CLINICAL PERSPECTIVE

What Is New?

- In the patient with non-valvular atrial fibrillation, non-vitamin K antagonist oral anticoagulants lower incidence risks of acute kidney injury, worsening renal function, doubling serum creatinine and end-stage renal disease compared with warfarin.

What Are the Clinical Implications?

- On non-valvular patients with atrial fibrillation, non-vitamin K antagonist oral anticoagulants should be the priority consideration to use for preventing kidney outcomes.
- These benefits might come from class effect or specific individual effect of non-vitamin K antagonist oral anticoagulants.
- More data to support this study are needed in the future.

Nonstandard Abbreviations and Acronyms

DOACs	direct oral anticoagulant
NOACs	non-vitamin K oral anticoagulant

has been the mainstay therapy of non-valvular AF.[4,5] In this regard, non-vitamin K oral anticoagulants (NOACs) are increasingly used for thromboembolism prevention in patients with non-valvular AF because of their favorable safety profile compared with warfarin, particularly lower bleeding risk, including intracranial hemorrhage.[6] Furthermore, the use of NOACs does not need drug level monitoring, resulting in improved patient compliance. According to the 2019 American Heart Association guideline,[4] NOACs have been approved and are now recommended in preference to warfarin in most of the patients with non-valvular AF.

Excessive doses of warfarin could cause acute kidney injury (AKI) or "warfarin-related nephropathy", the causes of which are still unestablished but might be mediated by glomerular bleeding and red blood cell cast obstruction.[7,8] Most but not all studies showed that NOACs, which do not have a direct effect on vitamin K, could cause lower incidence of AKI.[9–12] Besides AKI, chronic use of warfarin might gradually deteriorate renal function, possibly by increasing renovascular calcification.[13] This would cause progressive renal impairment in long-term outcome. Some earlier studies illustrated that NOACs, which can attenuate vascular inflammation, provided better long-term renal outcomes than warfarin.[10,14,15] Previous meta-analyses on these issues yielded contradictory results and did not extensively examine long-term renal outcomes.[16,17] In addition, there were several methodology-related drawbacks in these meta-analyses, including insufficient numbers of sample size, study designs, variation in the definition of renal outcomes, and drug-related issues in the studies.

The present systematic review and meta-analysis were conducted in patients with non-valvular AF to comprehensively compare short-term and long-term renal outcomes between warfarin and NOACs, including apixaban, dabigatran, edoxaban, and rivaroxaban.

METHODS

Data Sources and Searches

The data that support the findings of this study are available from the corresponding author upon reasonable request. The process of literature review as well as screening was systematically searched without linguistic restriction from January 1, 2000, to December 31, 2019. We electronically searched the databases of Medline, Scopus, and Cochrane Library to identify all potentially eligible studies that compared renal function or renal outcomes of any "non-vitamin K antagonist oral anticoagulant" or "NOAC" or "novel oral anticoagulants" or "direct oral anticoagulants or DOAC or dabigatran or edoxaban or rivaroxaban or apixaban. Furthermore, unpublished data were sought from ClinicalTrials.gov. The search was limited to the English language and focused on human studies.

Study Selection

We included studies if they were randomized clinical trials (RCTs), sub-analyses of RCTs, or observational cohort (prospective or retrospective) implicated with NOACs that reported about renal outcomes. Studies were excluded if they were publication types with no data, such as reviews, meta-analyses, case reports, editorial, abstracts, or editorial letters.

Interested Outcomes

We assessed the risk of renal outcomes in 4 aspects: First, AKI, defined as increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline or diagnosis code of AKI. Second, worsening renal function, defined as a decrease of >25%–30% in estimated glomerular filtration rate. Third, doubling serum creatinine, defined as changes from baseline at any time point during follow-up. Fourth, end-stage renal disease (ESRD), defined as estimated glomerular filtration rate <15 mL/min per 1.73 m^2, having kidney transplantation, or undergoing long-term dialysis. The incidence rates of all renal

outcomes were also determined. The short-term outcome in the present meta-analysis was defined as AKI while ESRD was designated for the long-term outcome.

Data Extraction, Quality Evaluation, and Bias Assessment

This study was separately reviewed by 2 independent reviewers (Patita Sitticharoenchai and Kullaya Takkavatakarn). If there were any disagreements that did not have a conclusion, the corresponding author (Paweena Susantitaphong) would make a consensus. The 2 reviewers independently searched and screened the eligibility of the studies and extracted information about study characteristics, renal outcomes, patient baseline characteristics, comorbidities, and follow-up period. If the renal outcomes or functions were not reported in the original publication or supplements, the data were extracted from the ClinicalTrials.gov.

The quality of the RCTs was evaluated according to the Jadad scale with a score between 0 (poor quality), and 5 (high quality) while the risk of bias of observational studies was determined by Newcastle-Ottawa quality assessment which the maximum score is 9 and 7 is the threshold for high quality. Publication bias was analyzed using the Egger test.

Statistical Analysis

The random-effects model was used, and the results were reported as pooled incidence and hazard ratios (HR) with 95% CI of AKI, worsening renal function, doubling serum creatinine, and ESRD.

Heterogeneity was evaluated by I^2 test, and the I^2 value of >50% demonstrated substantial heterogeneity. For any variables presenting with large heterogeneity, subgroup analysis was used to investigate the potential origin of the heterogeneity. To assess publication bias, funnel plots and the Egger test, which determines asymmetry of the funnel plot, were used and *P* value <0.05 indicates publication bias. Statistical analyses were performed using Comprehensive Meta-Analysis (version 2.0; Biostat, Englewood, NJ).

RESULTS

Characteristics of the Studies

The results of the electronic search and article selection were demonstrated in Figure 1. A total of 2017 potentially relevant citations were established, 1837 articles were assessed for abstract evaluation, and 44 articles were retrieved for full-text review. Finally, 18 articles fulfilled the suitable criteria, including 11 RCTs

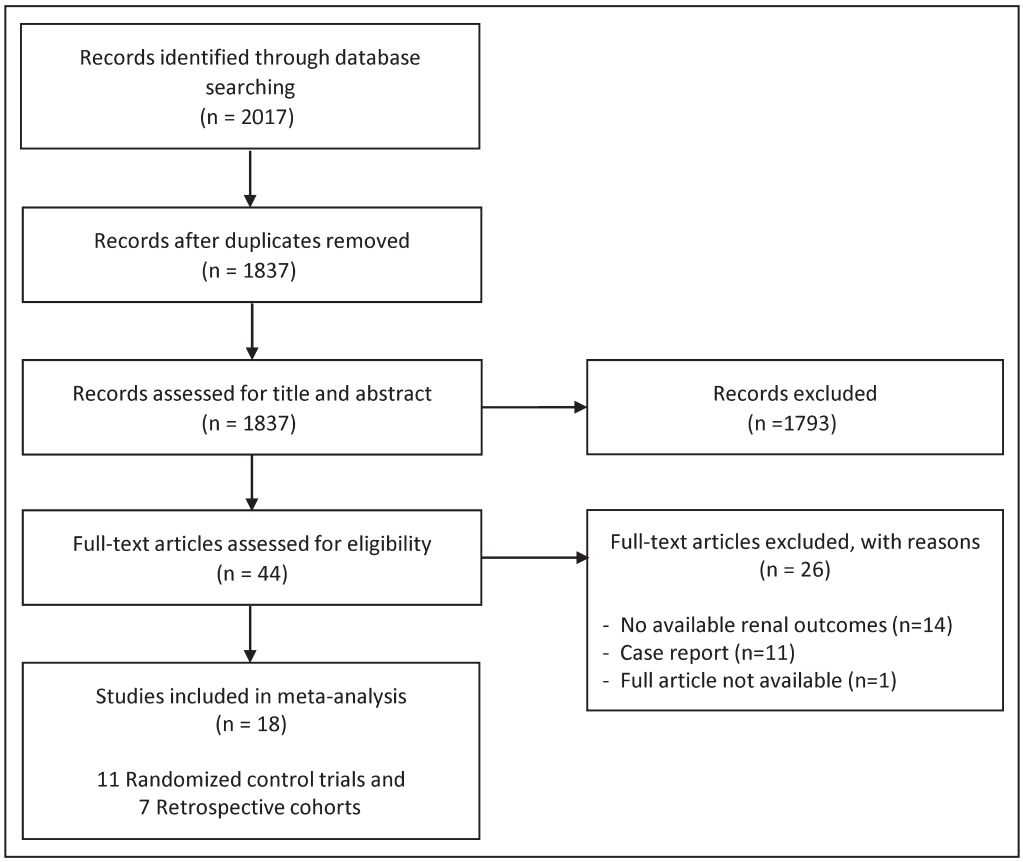

Figure 1. Study flowchart.
Flow diagram of the study demonstrating the selection process.

and 7 observational studies. Publication periods were from 2009 to 2019. A total of 285 201 patients were enrolled, 118 863 patients with warfarin and 166 338 patients with NOACs. The attribution of the 11 RCTs and 7 observational studies were detailed in Table 1. The follow-up duration was varied from 1 to 48 months. The majority of the population in all studies were men (62.9%) and age ranges were from 60 to 75 years old. Patient demographic data and comorbidities were comparable across the 18 studies.

Incidence Rate of AKI in NOACs and Warfarin Groups

By meta-analysis of 8 study arms,[10,11,32] the incidence rate of AKI in the NOACs group (apixaban, dabigatran, and rivaroxaban) was 9.8 per 100 person-year, (95% CI, 6.42–13.23) while the warfarin group showed the incidence rate of 14.13 per 100 person-year (95% CI, 6.61–21.66). Of note, the incidence rate of AKI was lowest in rivaroxaban 8.05 per 100 person-year (95% CI, 4.37–12.62), following by dabigatran 9.5 per 100 person-year (95% CI, −0.97–19.97), and apixaban 12.84 per 100 person-year (95% CI, −2.5–28.19).

Incidence Rate of Worsening Renal Function in NOACs and Warfarin Groups

By meta-analysis of 5 study arms,[9,26,27] the incidence rate of worsening renal function in the NOACs group (dabigatran, rivaroxaban, and apixaban) was 10.95 per 100 person-year (95% CI, 4.05–17.84) while the warfarin group exhibited a higher rate of 15.8 per 100 person-years (95% CI, 2.46–29.14).

Incidence Rate of Doubling Serum Creatinine in NOACs and Warfarin Groups

By meta-analysis of 3 study arms,[9] the incidence rate among the NOACs group (apixaban, dabigatran, and rivaroxaban) was 1.61 per 100 person-year (95% CI, 1.06–2.17) while the warfarin group demonstrated a higher rate of 3.43 per 100 person-years (95% CI, 2.78–4.22).

Incidence Rate of ESRD in NOACs and Warfarin Groups

By meta-analysis of 7 study arms,[9,10,28,32] the incidence rate among the NOACs group (apixaban, dabigatran, and rivaroxaban) was 1.42 per 100 person-years (95% CI, 0.75–2.09) while the warfarin group illustrated a higher rate of 2.63 per 100 person-years (95% CI, 0.93–4.32).

HR of NOACs on Acute Kidney Injury Compared With Warfarin

By meta-analysis of 28 study arms,[9-11,18-24,28-32] the risk of AKI was significantly lower in the NOACs group (HR, 0.70; 95% CI, 0.64–0.77; $P<0.001$). (Table 2) By subgroup analysis on types of medication, NOACs were associated with a significantly lower risk of AKI compared with warfarin; HR, 0.66 (95% CI, 0.54–0.81; $P<0.001$) for apixaban, HR, 0.66 (95% CI, 0.57–0.76.; $P<0.001$) for dabigatran, and HR, 0.73 (95% CI, 0.63–0.85; $P<0.001$) for rivaroxaban. No significant difference in risk of AKI was found among patients using edoxaban compared with warfarin (HR, 0.91; 95% CI, 0.71–1.17; $P=0.479$). (Table 3, and Figure 2).

Furthermore, in the NOACs group, the risk of AKI was significantly lower in patients with or without CKD (HR, 0.60; [95% CI, 0.48–0.75; $P<0.001$], and HR, 0.64 [95% CI, 0.54–0.75; $P<0.001$], respectively). The significantly lower risk of AKI in the NOACs group was noted only in patients with the follow-up duration of >3 months (HR, 0.71; 95% CI, 0.65–0.77; $P<0.001$]). (Table 3).

HR of NOACs on the Incidence of Worsening Renal Function

By meta-analysis of 7 study arms,[9,25-27] the risk of worsening renal function was significantly lower in the NOACs group compared with the warfarin group (HR, 0.83; 95% CI, 0.73–0.95; $P=0.006$). (Table 2 and Figure 3).

HR of NOACs on the Incidence of Doubling Serum Creatinine

By meta-analysis of 3 study arms,[9] there was a significantly lower risk of doubling serum creatinine in the NOACs group when compared with the warfarin group (HR, 0.58; 95% CI, 0.41–0.82; $P=0.002$) (Table 2 and Figure 4).

HR of NOACs on the Incidence of ESRD

By meta-analysis of 5 study arms,[9,10,32] a significantly lower risk of ESRD in the NOACs group was observed when compared with the warfarin group (HR, 0.82; 95% CI, 0.78–0.86; $P<0.001$). (Table 2 and Figure 5).

Since there were only 4, 1, and 3 studies having data of worsening renal function, doubling serum creatinine, and ESRD, there were insufficient information to analyze for the impact of individual NOACs on these renal outcomes.

Publication Bias

The funnel plot (Figures S1 through S4) for the interested outcomes was symmetric, and the Egger test was not significant in all interested outcomes, suggesting less susceptibility to publication bias.

DISCUSSION

The present meta-analysis, which included 285 201 patients from 11 RCTs and 7 observational studies,

Table 1. Characteristics of the Studies Included in the Present Meta-Analysis

Included Study	Publication, y	Study Type	Medication	Total Number	Age, y (Mean)	Men (%)	HF (%)	Hypertension (%)	DM (%)	Stroke (%)	History of MI (%)	CHADS2/ CHA2DS2VASc score	Follow-Up Time (mo)	Renal Outcomes
Connolly et al[18]	2009	RCT	Dabigatran	18 113	71.5	63.6	31.96	78.86	23.3	20	16.6	2.13	24	AKI
Granger et al[19]	2011	RCT	Apixaban	18 201	70	64.75	35.45	87.5	24.95	19.45	14.2	2.1	21.6	AKP
Patel et al[20]	2011	RCT	Rivaroxaban	14 264	73	60.3	62.45	90.55	39.95	54.75	17.3	3.47	19.6	AKI
Hori et al[21]	2012	RCT	Rivaroxaban	1280	71.1	80.5	40.8	79.5	38	N/A	7.7	3.25	30	AKI
Giugliano et al[22]	2013	RCT	Edoxaban	21 105	70.6	62.07	57.43	93.6	36.13	28.3	N/A	2.8	12	AKI, ESRD
Ezekowitz et al[23]	2014	RCT	Rivaroxaban	1504	64.9	72.7	N/A	N/A	N/A	N/A	N/A	2.3	1	AKI
Gibson et al[24]	2015	RCT	Rivaroxaban	2124	70.1	74.4	25.35	74.33	30.5	N/A	22.4	1.5	12	AKI
Böhm et al[25]	2015	RCT	Dabigatran	16 490	71.4	64.4	31.7	78.73	23.16	21.9	16.33	2.13	30	WRF
Fordyce et al[26]	2016	RCT	Rivaroxaban	12 612	73	61	62	90	40	55	17	3.5	19.6	WRF
Naganuma et al[27]	2016	Cohort	Apixaban, Dabigatran, Rivaroxaban	819	70.79	65.83	18.33	66.37	32.49	25.52	17.45	N/A	24	WRF
Chan et al[28]	2016	Cohort	Dabigatran	19 932	73.24	58.2	18	86	44	27.3	3.8	3.77	48	AKI, ESRD
Yao et al[9]	2017	Cohort	Apixaban, Dabigatran, Rivaroxaban	9769	72.6	55.1	34.1	91.8	44.4	16.4	14.2	4.1	24	AKI, WRF Doubling creatinine, ESRD
Calkins et al[29]	2018	RCT	Dabigatran	676	59.3	74.3	10.25	54.05	10.1	3	12.6	2.1	2	AKI
Ezekowitz et al[30]	2018	RCT	Apixaban	1500	64.6	66.8	6.6	65.15	19.6	6.6	N/A	2.4	3	AKI
Shin et al[31]	2018	Cohort	Apixaban, Dabigatran, Rivaroxaban	6412	72	53	N/A	N/A	N/A	N/A	N/A	N/A	N/A	AKI
Chan et al[11]	2018	Cohort	Apixaban, Dabigatran, Rivaroxaban	75 221	71.48	58.37	18.25	79.63	38.5	15	13.38	3.21	8	AKI
Hernandez et al[32]	2019	Cohort	Rivaroxaban	21 682	70	63.7	29.8	85.5	N/A	8.6	4.65	3	20	AKI, ESRD
Coleman et al[10]	2019	Cohort	Rivaroxaban	72 599	69	58.37	23.55	73.85	29.7	7.1	3.2	3	21	AKI, ESRD
Overall data	2009–2019	RCT and Cohort	Apixaban, Dabigatran, Rivaroxaban, Edoxaban	285 201	69.87	62.9	28.3	81	29.8	19.2	10.3	2.8	20	AKI, WRF, Doubling creatine, ESRD

AKI indicates acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal failure; HF, heart failure; MI, myocardial infarction; and RCT, randomized control trial.

Table 2. Primary Analysis Examining the Renal Outcomes in Patients Using NOACs Versus Warfarin

Outcome	HR	Lower Bound 95% CI	Upper Bound 95% CI	*P* Value	I^2 Index (%)	Egger Test
AKI (all)	0.70	0.64	0.77	<0.001	83.37	0.439
WRF	0.83	0.73	0.95	0.006	75.57	0.293
Doubling serum creatinine	0.58	0.41	0.82	0.002	0	0.376
ESRD	0.82	0.78	0.86	<0.001	0	0.369

AKI indicates acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NOACs, non-vitamin K oral anticoagulants; and WRF, worsening renal function.

was conducted to compare short-term and long-term renal outcomes, represented by AKI and ESRD, respectively, in non-valvular patients with AF treated with warfarin (n=118 863) and NOACs (n=166 338). The incidence rates of all renal outcomes were significantly less in NOAC users. The use of NOACs could provide a significantly lower hazard ratio of the risk of AKI (*P*<0.001), worsening renal function (*P*=0.006), doubling serum creatinine (*P*=0.002), and ESRD (*P*<0.001) when compared with warfarin (Table 2).

Non-valvular AF contributes ≈90% of the whole AF.[33] At present, anticoagulant therapy is the standard treatment of AF for stroke prevention. Initially, warfarin is most commonly prescribed in non-valvular AF.[34,35] However, several following studies had reported that warfarin could induce AKI known as warfarin-related nephropathy.[7,36–39] Kidney biopsy indicated that warfarin might cause AKI mainly via bleeding in glomeruli, resulting in red blood cell obstruction in tubular lumens.[36,40,41] A previous study reported that the incidence of warfarin-induced AKI was ≈25% among warfarin users, particularly in patients receiving high-dose warfarin prescription.[42] Of interest, the incidence of AKI was progressively increased depending on the degree of impairment of baseline renal function. In this regard, there was a 14-fold increase in risk of developing AKI among patients with stage 3 CKD.[43]

Table 3. Subgroup Analysis Examining the Renal Outcomes in Patients Using NOACs Versus Warfarin

Outcome	HR	Lower Bound 95% CI	Upper Bound 95% CI	*P* Value	I^2 Index (%)
AKI (apixaban)	0.66	0.54	0.81	<0.001	83.40
AKI (dabigatran)	0.66	0.57	0.76	<0.001	74.83
AKI (edoxaban)	0.91	0.71	1.17	0.479	0
AKI (rivaroxaban)	0.73	0.63	0.85	<0.001	86.08
AKI (≤3 mo follow-up)	0.27	0.06	1.17	0.081	0
AKI (>3 mo follow-up)	0.71	0.65	0.77	<0.001	84.96
AKI (among CKD population)	0.60	0.48	0.75	<0.001	93.77
AKI (among non-CKD population)	0.64	0.54	0.75	<0.001	90.73

AKI indicates acute kidney injury; CKD, chronic kidney disease; NOACs, non-vitamin K oral anticoagulants; and HR, hazard ratio.

NOACs have several pharmacologic advantages over warfarin, including rapid onset, predictable pharmacokinetics, and lower bleeding complications.[44] At present, NOACs are the main medication used in non-valvular AF.[4] Nonetheless, certain case reports revealed that NOACs were also associated with AKI by the same mechanism as warfarin-related nephropathy.[45–47]

On AKI in the present meta-analysis, NOACs provided a lower incidence of AKI and a lesser hazard ratio of the risk of AKI when compared with warfarin (Table 2). Of note, the consistency of the results could also be observed with individual NOACs, apixaban, dabigatran, and rivaroxaban, except for edoxaban (Table 3). The negative result of the lower risk of edoxaban might result from the fact that there was only 1 edoxaban-related RCT in this meta-analysis. This would result in the underpowered capability to demonstrate statistical efficiency.

Under normal homeostasis, matrix Gla protein, which is a vitamin K dependent protein, plays an important role in vascular calcification inhibition.[48,49] Therefore, long-term use of vitamin K antagonists like warfarin could increase vascular calcification, possibly leading to development of CKD and accelerating CKD progression.[7,13] On the contrary, NOACs have no interaction with vitamin K. Besides, previous studies demonstrated the effect of NOACs on the trend of plaque regression and attenuation of vascular inflammation.[15,50,51] Therefore, NOACs might yield a protective effect on renovascular calcification.[50,52]

In the present meta-analysis, NOACs could significantly reduce the hazard risk ratio on the incidences of worsening renal function, doubling serum creatinine, and ESRD (Table 2). The contradictory effects on renovascular calcification of NOACs and warfarin could explain the above results. As stated earlier, the prevalence of AF is rising in patients with CKD.[2] The presence of CKD results in an increased risk of thromboembolism (HR, 1.46; 95% CI, 1.2–1.76; *P*=0.0001), particularly in case of ESRD (HR, 1.83; 95% CI, 1.56–2.14,

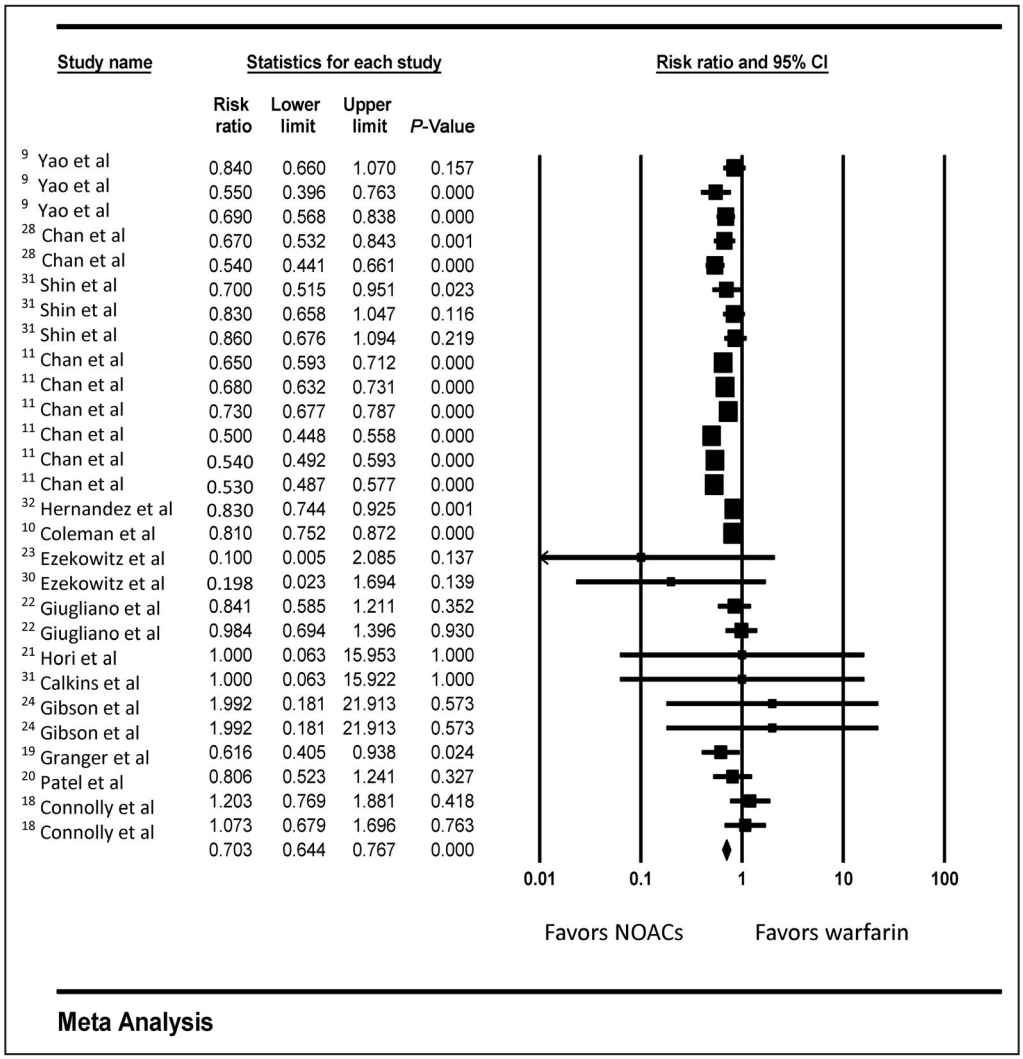

Figure 2. Forest plot of individual study displaying the hazard ratio for acute kidney injury.
NOACs indicates non-vitamin K oral anticoagulant.

P<0.00001).[26] Therefore, the superior advantage of NOACs over warfarin in retarding progression of renal impairment would attenuate the development of AF and thromboembolism in patients with CKD. As formerly mentioned, the incidence of AKI is progressively dependent on the severity of renal impairment.[11] As such, the greater benefit of NOACs over warfarin in preserving long-term renal function would lessen the incidence in developing AKI following treatment with NOACs.

Indeed, an earlier meta-analysis by Caldeira et al,[16] involving 75 100 patients from 10 RCTs, demonstrated that NOACs yielded comparable risk of renal failure compared with vitamin K antagonist/low-molecular weight heparin. However, there were several flaws in such meta-analysis, including insufficient sample size in RCTs, a wide range of drug use indications (comprising AF, venous thromboembolism, and hip/knee arthroplasty), and use of vitamin K antagonist and low-molecular weight heparin as combined controls, all of which might cause underestimation or overestimation of the risk of renal failure. In a recent meta-analysis by Zhang et al,[17] involving 189 483 patients from 11 RCTs and 3 observational studies, NOACs provided a lower risk of renal impairment compared with vitamin K antagonists or acetylsalicylic acid. Although, the meta-analysis by Zhang et al[17] seemed to provide more reliable and updated information than the study by Caldeira et al,[16] the definition of renal impairment in the meta-analysis by Zhang et al[17] was varied, including acute tubular necrosis, nephritis, nephrotic syndrome, and post-renal failure. The variations of definition might also lead to heterogeneity of the results. In addition, long-term renal outcomes were not comprehensively determined in such meta-analysis. Furthermore, vitamin K antagonists and salicylic acid were used as the combined control.[17]

The present meta-analysis, which obviously included more patients than the 2 previous meta-analyses, has

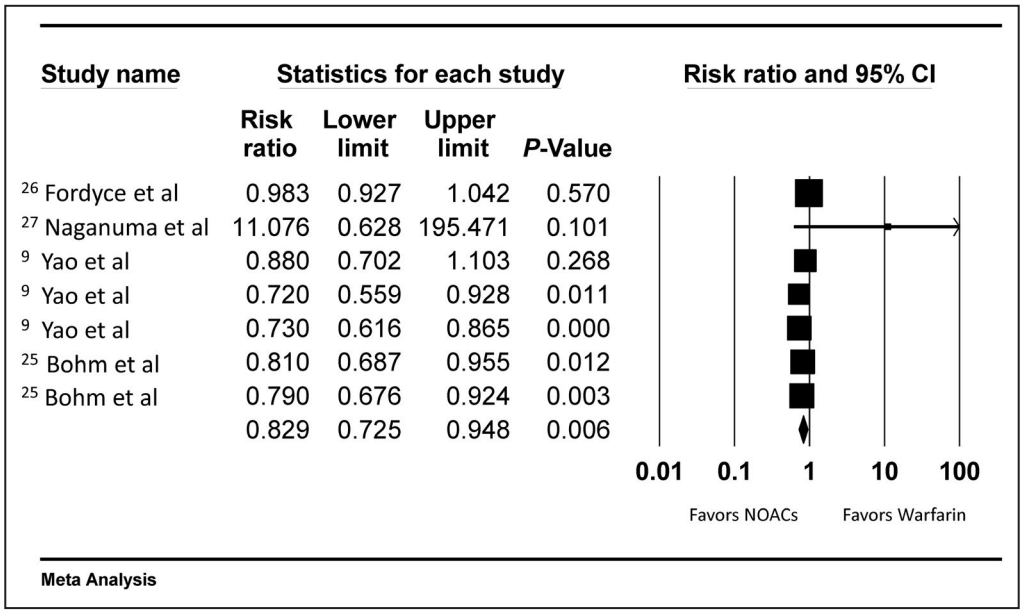

Figure 3. Forest plot of individual study displaying the hazard ratio for worsening renal function.
NOACs indicates non-vitamin K oral anticoagulant.

several strengths and interesting points compared with the earlier studies. First, to our knowledge, this is the first meta-analysis that extensively evaluated not only short-term outcomes in the aspect of AKI but also carefully revealed the long-term outcomes of kidney function, including worsening renal function, doubling serum creatinine, and ESRD. Second, we conducted an extensive and up-to-date literature review, including many RCTs and good-quality observational studies. Third, the previous meta-analyses reported a composite outcome in terms of renal impairment, in which the definition of renal impairment was not clearly identified and varied among the included studies.[16,17] Fourth, our study also evaluated subgroup analysis in the timing of the follow-up period and found that the development of AKI events was lower in the NOACs group after receiving medications for >3 months. Fifth, we also demonstrated that AKI events were lower in the NOACs groups in both patients with normal kidney function and CKD.

Admittedly, there were some limitations in the present meta-analysis. First, there was the high I^2

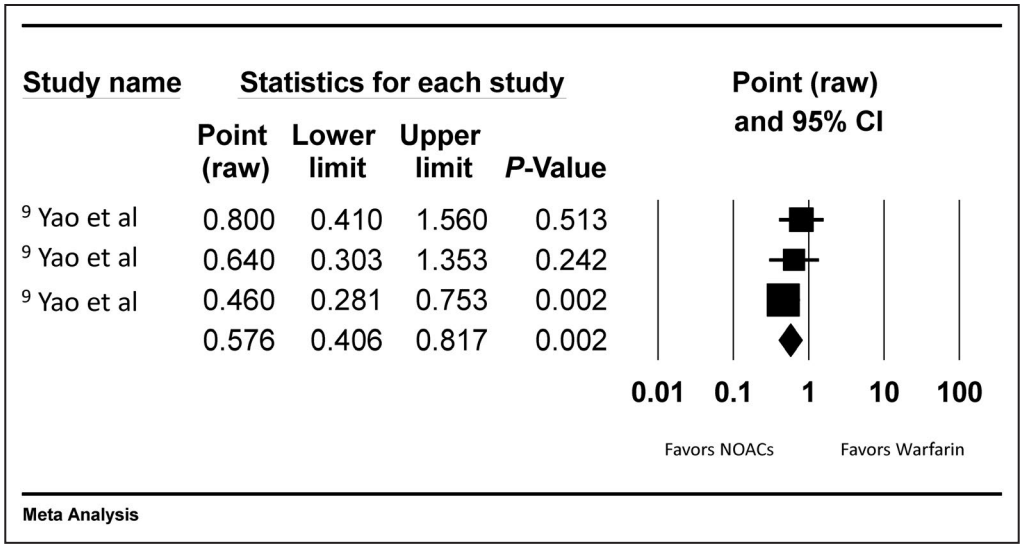

Figure 4. Forest plot of individual study displaying the hazard ratio for doubling serum creatinine.
NOACs indicates non-vitamin K oral anticoagulant.

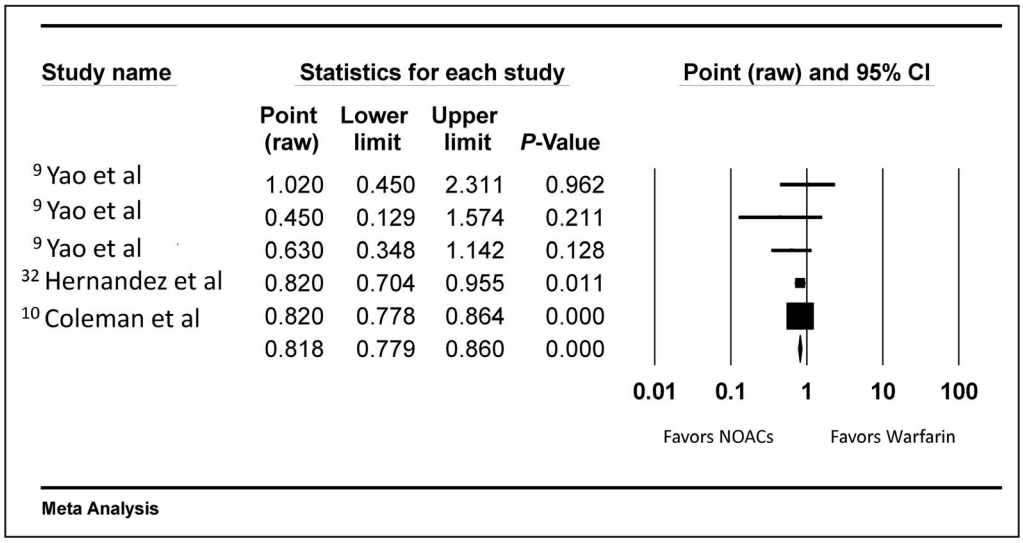

Figure 5. Forest plot of individual study displaying the hazard ratio for end-stage renal disease.
NOACs indicates non-vitamin K oral anticoagulant.

value, which represented considerable heterogeneity. Second, some papers demonstrated only the change of renal functions in short-term follow-up that we cannot include in our meta-analysis in terms of incidence of ESRD.[23,29,30] Third, the definitions of worsening renal outcome and estimated glomerular filtration rate equation were varied among the studies, both of which might affect the validity of the results. Lastly, the clinical outcomes per each NOAC were only described in AKI. Unfortunately, the data about other outcomes especially incidence of ESRD are insufficient to analyze for individual NOACs. Therefore, we cannot make the final conclusion that these benefits might come from class effect or specific individual effect of NOAC.

CONCLUSIONS

In patients with non-valvular AF, patients treated with NOACs have a lower risk of both AKI and ESRD when compared with warfarin. These benefits might come from class effect or specific individual effect of NOAC. More data to support this knowledge are needed in the future.

ARTICLE INFORMATION

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Affiliations

From the Division of Cardiology, Department of Medicine, Faculty of Medicine (P.S., S.B.) and Division of Nephrology, Department of Medicine, Faculty of Medicine (K.T., K.P., S.E., P.S.), King Chulalongkorn Memorial Hospital, Bangkok, Thailand; and Research Unit for Metabolic Bone Disease in CKD patients, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (P.S.).

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None.

Supplementary Material

Figures S1–S4

REFERENCES

1. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circ Cardiovasc Qual Outcomes*. 2012;5:85–93. DOI: 10.1161/CIRCOUTCOMES.111.962688.
2. Dang D, Arimie R, Haywood LJ. A review of atrial fibrillation. *J Natl Med Assoc*. 2002;94:1036–1048.
3. Iwasaki YK, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: implications for management. *Circulation*. 2011;124:2264–2274. DOI: 10.1161/CIRCULATIONAHA.111.019893.
4. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeions. *Circulation*. 2019;140:e125–e151. DOI: 10.1161/CIR.0000000000000665.
5. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, 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*. 2018;39:1330–1393. DOI: 10.1093/eurheartj/ehy136.
6. Greenspon AJ. A review of oral anticoagulants in patients with atrial fibrillation. *J Postgrad Med*. 2012;124:7–16. DOI: 10.3810/pgm.2012.11.2608.
7. Mendonca S, Gupta D, Valsan A, Tewari R. Warfarin related acute kidney injury: a case report. *Indian J Nephrol*. 2017;27:78–80. DOI: 10.4103/0971-4065.177142.
8. Golla A, Goli R, Nagalla V, Kiran B, Raju DSB, Uppin M. Warfarin-related nephropathy. *Indian J Nephrol*. 2018;28:378–381. DOI: 10.4103/ijn.IJN_3_17.
9. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, Noseworthy PA. Renal outcomes in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2017;70:2621–2632. DOI: 10.1016/j.jacc.2017.09.1087.
10. Coleman CI, Kreutz R, Sood N, Bunz TJ, Meinecke AK, Eriksson D, Baker WL. Rivaroxaban's impact on renal decline in patients with

nonvalvular atrial fibrillation: a US marketscan claims database analysis. *Clin Appl Thromb Hemost*. 2019;25:1076029619868535. DOI: 10.1177/1076029619868535.
11. Chan YH, Yeh YH, Hsieh MY, Chang CY, Tu HT, Chang SH, See LC, Kuo CF, Kuo CT. The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: a nationwide cohort study in Taiwan. *Int J Cardiol*. 2018;265:83–89. DOI: 10.1016/j.ijcard.2018.02.075.
12. Patel S, Hossain MA, Ajam F, Patel M, Nakrani M, Patel J, Alhillan A, Hammoda M, Alrefaee A, Levitt M, et al. Dabigatran-induced acute interstitial nephritis: an important complication of newer oral anticoagulation agents. *J Clin Med Res*. 2018;10:791–794. DOI: 10.14740/jocmr3569w.
13. Poterucha TJ, Goldhaber SZ. Warfarin and vascular calcification. *Am J Med*. 2016;129:635.e1–e4. DOI: 10.1016/j.amjmed.2015.11.032.
14. Kim J-B, Joung HJ, Lee JM, Woo JS, Kim W-S, Kim KS, Lee KH, Kim W. Evaluation of the vascular protective effects of new oral anticoagulants in high-risk patients with atrial fibrillation (PREFER-AF): study protocol for a randomized controlled trial. *Trials*. 2016;17:422. DOI: 10.1186/s13063-016-1541-8.
15. Nakase T, Moroi J, Ishikawa T. Anti-inflammatory and antiplatelet effects of non-vitamin K antagonist oral anticoagulants in acute phase of ischemic stroke patients. *Clin Transl Med*. 2018;7:2. DOI: 10.1186/s40169-017-0179-9.
16. Caldeira D, Goncalves N, Pinto FJ, Costa J, Ferreira JJ. Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf*. 2015;24:757–764. DOI: 10.1002/pds.3791.
17. Zhang C, Gu ZC, Ding Z, Shen L, Pan MM, Zheng YL, Lin HW, Pu J. Decreased risk of renal impairment in atrial fibrillation patients receiving non-vitamin K antagonist oral anticoagulants: a pooled analysis of randomized controlled trials and real-world studies. *Thromb Res*. 2019;174:16–23. DOI: 10.1016/j.thromres.2018.12.010.
18. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. DOI: 10.1056/NEJMoa0905561.
19. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. DOI: 10.1056/NEJMoa1107039.
20. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. DOI: 10.1056/NEJMoa1009638.
21. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study. *Circ J*. 2012;76:2104–2111. DOI: 10.1253/circj.cj-12-0454.
22. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. DOI: 10.1056/NEJMoa1310907.
23. Ezekowitz M, Cappato R, Klein A, Camm J, Ma C-S, Le Heuzey J-Y, Talajic M, Scanavacca M, Vardas P, Kirchhof P, et al. Rationale and design of the X-VERT trial: a comparison of oral rivaroxaban once daily with dose-adjusted vitamin K antagonists in patients with nonvalvular atrial fibrillation undergoing elective cardioversion. *Am Heart J*. 2014;167:646–652. DOI: 10.1016/j.ahj.2013.12.024.
24. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F, Wildgoose P, van Eickels M, Lip GYH, Cohen M, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *Am Heart J*. 2015;169:472–478.e5. DOI: 10.1016/j.ahj.2014.12.006.
25. Böhm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY Trial. *J Am Coll Cardiol*. 2015;65:2481–2493. DOI: 10.1016/j.jacc.2015.03.577.
26. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, Mahaffey KW, et al. On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin. *Circ J*. 2016;134:37–47. DOI: 10.1161/CIRCULATIONAHA.116.021890.
27. Naganuma M, Shiga T, Nagao T, Maruyama K, Suzuki A, Murasaki K, Hagiwara N. Renal function and treatment persistence with non-vitamin K antagonist oral anticoagulants in Japanese patients with atrial fibrillation: a single-center experience. *J Clin Pharmacol Ther*. 2016;47:115–122.
28. Chan YH, Yeh YH, See LC, Wang CL, Chang SH, Lee HF, Wu LS, Tu HT, Kuo CT. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. *J Am Coll Cardiol*. 2016;68:2272–2283. DOI: 10.1016/j.jacc.2016.08.063.
29. Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. 2017;376:1627–1636. DOI: 10.1056/NEJMoa1701005.
30. Ezekowitz MD, Pollack CV, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J*. 2018;39:2959–2971. DOI: 10.1093/eurheartj/ehy148.
31. Shin JI, Luo S, Alexander GC, Inker LA, Coresh J, Chang AR, Grams ME. Direct oral anticoagulants and risk of acute kidney injury in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;71:251–252. DOI: 10.1016/j.jacc.2017.10.089.
32. Hernandez AV, Bradley G, Khan M, Fratoni A, Gasparini A, Roman YM, Bunz TJ, Eriksson D, Meinecke AK, Coleman CI. Rivaroxaban versus warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. *Eur Heart J Qual Care Clin Outcomes*. 2020;6:301–307. DOI: 10.1093/ehjqcco/qcz047.
33. Blustin JM, McBane RD, Ketha SS, Wysokinski WE. Distribution of thromboembolism in valvular versus non-valvular atrial fibrillation. *Expert Rev Cardiovasc Ther*. 2014;12:1129–1132. DOI: 10.1586/14779072.2014.960851.
34. Ikeda T, Yasaka M, Kida M, Imura M. A survey of reasons for continuing warfarin therapy in the era of direct oral anticoagulants in Japanese patients with atrial fibrillation: the SELECT study. *Patient Prefer Adherence*. 2018;12:135–143. DOI: 10.2147/PPA.S152584.
35. Hansen PW, Sehested TSG, Fosbol EL, Torp-Pedersen C, Kober L, Andersson C, Gislason GH. Trends in warfarin use and its associations with thromboembolic and bleeding rates in a population with atrial fibrillation between 1996 and 2011. *PloS One*. 2018;13:e0194295. DOI: 10.1371/journal.pone.0194295.
36. Brodsky SV, Satoskar A, Chen J, Nadasdy G, Eagen JW, Hamirani M, Hebert L, Calomeni E, Nadasdy T. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. *Am J Kidney Dis*. 2009;54:1121–1126. DOI: 10.1053/j.ajkd.2009.04.024.
37. Ozcan A, Ware K, Calomeni E, Nadasdy T, Forbes R, Satoskar AA, Nadasdy G, Rovin BH, Hebert LA, Brodsky SV. 5/6 nephrectomy as a validated rat model mimicking human warfarin-related nephropathy. *Am J Nephrol*. 2012;35:356–364. DOI: 10.1159/000337918.
38. Ryan M, Ware K, Qamri Z, Satoskar A, Wu H, Nadasdy G, Rovin B, Hebert L, Nadasdy T, Brodsky SV. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. *Nephrol Dial Transplant*. 2014;29:2228–2234. DOI: 10.1093/ndt/gft380.
39. Golbin L, Vigneau C, Touchard G, Thervet E, Halimi J-M, Sawadogo T, Lagoutte N, Siohan P, Zagdoun E, Hertig A, et al. Warfarin-related nephropathy induced by three different vitamin K antagonists: analysis of 13 biopsy-proven cases. *Clin Kidney J*. 2017;10:381–388. DOI: 10.1093/ckj/sfw133.
40. Reynaud F, Giraud P, Cisterne JM, Verdier D, Kouchakipour Z, Hermelin A, Modesto-Segonds A, Bagheri H, Pourrat J. Acute mmune-allergic interstitial nephritis after treatment with fluindione. Seven cases. *Nephrol Ther*. 2009;5:292–298.
41. Fanola CL, Mooney D, Cowan AJ, Ko D, Sisson EK, Henault LE, Tripodis Y, Hylek EM. Incidence of severe renal dysfunction among individuals taking warfarin and implications for non-vitamin K oral anticoagulants. *Am Heart J*. 2017;184:150–155. DOI: 10.1016/j.ahj.2016.08.017.
42. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, Bhatt UY, Hebert LA. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int*. 2011;80:181–189. DOI: 10.1038/ki.2011.44.

43. Fanola CL, Mooney D, Cowan AJ, Ko D, Sisson EK, Henault LE, Tripodis Y, Hylek EM. Incidence of severe renal dysfunction among individuals taking warfarin and implications for non–vitamin K oral anticoagulants. *Am Heart J*. 2017;184:150–155. DOI: 10.1016/j.ahj.2016.08.017.
44. Gelosa P, Castiglioni L, Tenconi M, Baldessin L, Racagni G, Corsini A, Bellosta S. Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs). *Pharmacol Res*. 2018;135:60–79. DOI: 10.1016/j.phrs.2018.07.016.
45. Brodsky SV, Mhaskar NS, Thiruveedi S, Dhingra R, Reuben SC, Calomeni E, Ivanov I, Satoskar A, Hemminger J, Nadasdy G, et al. Acute kidney injury aggravated by treatment initiation with apixaban: another twist of anticoagulant-related nephropathy. *Kidney Res Clin Pract*. 2017;36:387–392. DOI: 10.23876/j.krcp.2017.36.4.387.
46. Awesat J, Sagy I, Haviv YS, Rabinovich A, Jotkowitz A, Shleyfer E, Barski L. Dabigatran-induced nephropathy and its successful treatment with Idarucizumab—case report and literature review. *Thromb Res*. 2018;169:120–122. DOI: 10.1016/j.thromres.2018.07.019.
47. DiMaria C, Hanna W, Murone J, Reichart J. Direct oral anticoagulant and AKI: apixaban-induced acute interstitial nephritis. *BMJ Case Rep*. 2019;12:e230371. DOI: 10.1136/bcr-2019-230371.
48. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, Karsenty G. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997;386:78–81. DOI: 10.1038/386078a0.
49. Chatrou ML, Winckers K, Hackeng TM, Reutelingsperger CP, Schurgers LJ. Vascular calcification: the price to pay for anticoagulation therapy with vitamin K-antagonists. *Blood Rev*. 2012;26:155–166. DOI: 10.1016/j.blre.2012.03.002.
50. Sparkenbaugh EM, Chantrathammachart P, Mickelson J, van Ryn J, Hebbel RP, Monroe DM, Mackman N, Key NS, Pawlinski R. Differential contribution of Fxa and thrombin to vascular inflammation in a mouse model of sickle cell disease. *Blood*. 2014;123:1747–1756. DOI: 10.1182/blood-2013-08-523936.
51. Horinouchi Y, Ikeda Y, Fukushima K, Imanishi M, Hamano H, Izawa-Ishizawa Y, Zamami Y, Takechi K, Miyamoto L, Fujino H, et al. Renoprotective effects of a factor Xa inhibitor: fusion of basic research and a database analysis. *Sci Rep*. 2018;8:10858. DOI: 10.1038/s41598-018-29008-2.
52. Lee IO, Kratz MT, Schirmer SH, Baumhakel M, Bohm M. The effects of direct thrombin inhibition with dabigatran on plaque formation and endothelial function in apolipoprotein E-deficient mice. *J Pharmacol Exp Ther*. 2012;343:253–257. DOI: 10.1124/jpet.112.194837.

SUPPLEMENTAL MATERIAL

Figure S1. Funnel plot for the risk of acute kidney injury.

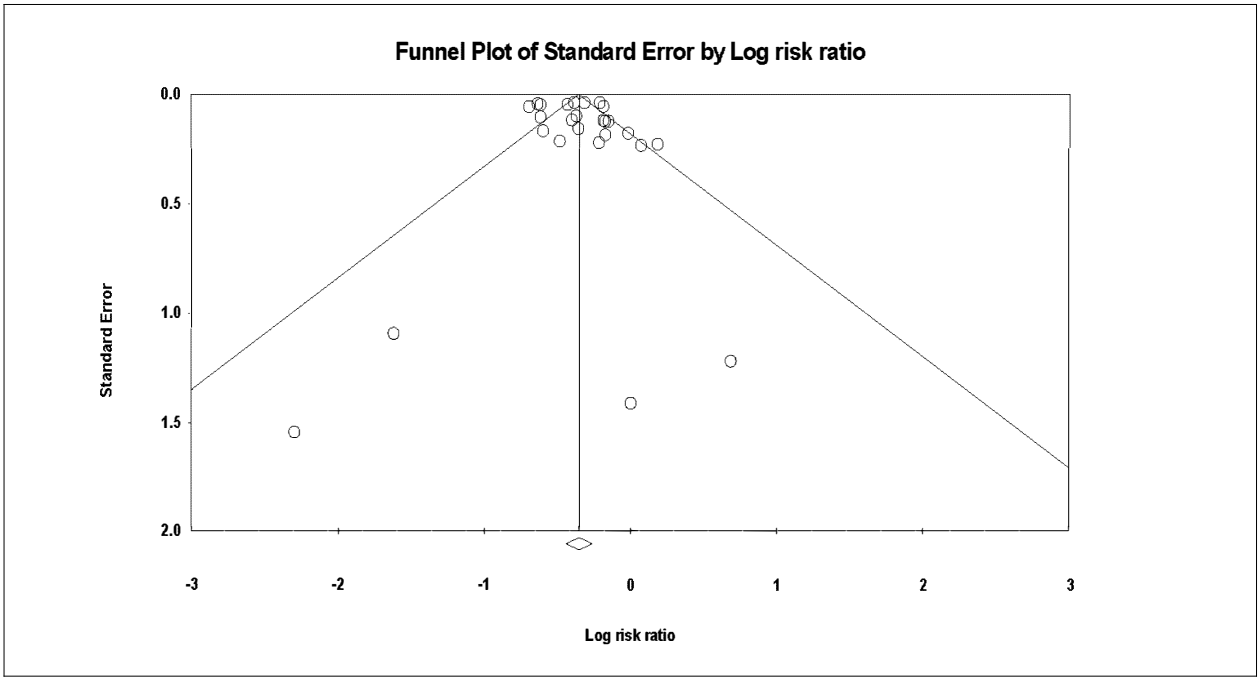

Figure S2. Funnel plot for the incidence of worsening renal function.

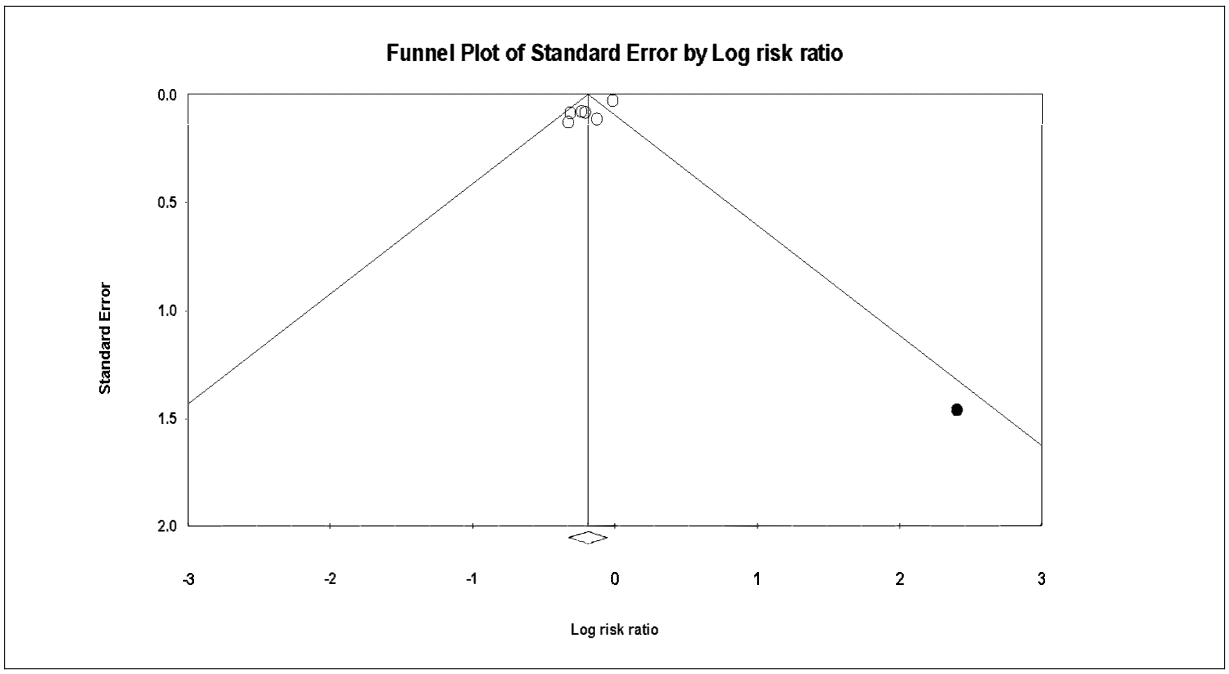

Figure S3. Funnel plot for the incidence of doubling serum creatinine.

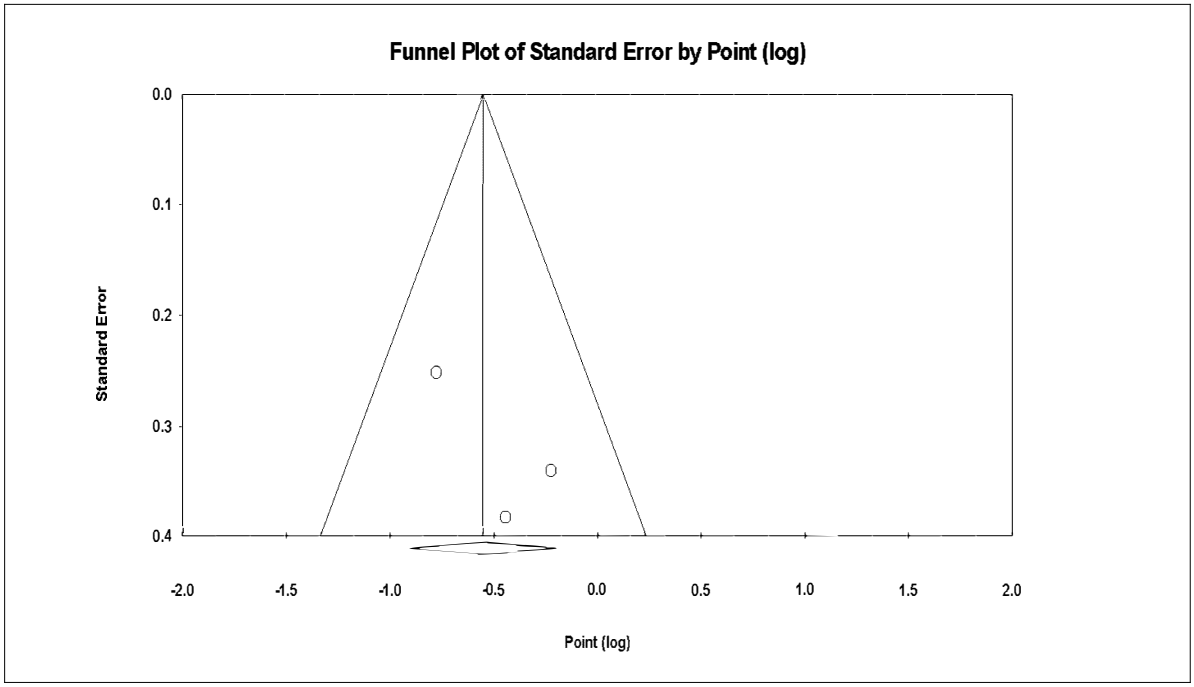

Figure S4. Funnel plot for the incidence of End stage renal disease.