Original Article

Net clinical benefit of non-vitamin K antagonist oral anticoagulants in atrial fibrillation and chronic kidney disease: a trade-off analysis from four phase III clinical trials

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Background: Atrial fibrillation (AF) is quite prevalent in patient with chronic kidney disease (CKD). This study mainly investigated the net clinical benefit (NCB) property of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin in patients with AF and CKD by a pooled-analysis.

Methods: A comprehensive search of Medline, Embase, Cochrane Library and Clinical Trials.gov Website was performed for eligible randomized controlled trials (RCTs) reporting the efficacy and safety outcomes according to renal function of NOACs. Pre-specified outcomes and their number of patients needed to treat (NNT), including stroke/systemic embolism (SSE), major bleeding, and all-cause death, were evaluated using a random-effects model. NCB that balanced SSE and major bleeding was calculated using Singer's method.

Results: Four phase III clinical trials including 70,952 patients were enrolled, 45,265 (64%) with CKD, and 25,687 (36%) without CKD; 41,942 (59%) taking NOACs and 29,010 (41%) taking warfarin. Risks of SSE [relative risk (RR): 0.80, 95% confidence interval (CI): 0.73–0.88, P<0.01], major bleeding (RR: 0.79, 95% CI: 0.66–0.96, P=0.017), and all-cause death (RR: 0.91, 95% CI: 0.84–0.99, P=0.031) were significantly lower in CKD patients with NOACs than those with warfarin, accompanying with a high absolute risk reduction (NNT: 182 for SSE; 122 for major bleeding; 196 for all-cause death). While NOACs were not superior to warfarin on SSE, major bleeding, and all-cause death in patients without CKD, the NCB of NOACs versus warfarin was progressively increased with the deterioration of renal function (NCB: 0.72 for no CKD, 1.59 for mild CKD, 2.74 for moderate CKD). Sensitivity analyses did not significantly affect the primacy results.

Conclusions: NOACs, compared with warfarin, provide a better clinical profile on SSE, major bleeding, all-cause death, and NCB in CKD patients.

Keywords: Atrial fibrillation (AF); chronic kidney disease (CKD); oral anticoagulants; non-vitamin K antagonist oral anticoagulants (NOACs); net clinical benefit (NCB)

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Introduction

The prevalence of atrial fibrillation (AF) is high in patients with chronic kidney disease (CKD) (1). CKD shows an increased risk for cardiovascular disease, meanwhile is itself an important predictor of thrombosis and hemorrhage (2). Additionally, CKD is widely regarded as a risk factor for the low time in therapeutic range (TTR), and superimposed platelet dysfunction in AF participants treated with warfarin (3). Therefore, AF patients with the morbid state of CKD are even at an increased risk for stroke or systemic embolism and hemorrhage.

Non-vitamin K antagonist oral anticoagulants (NOACs), with favorable efficacy and safety profiles, confer practical advantages in AF (4). In 2018, data from Taiwan showed that NOACs accounted for about 73% of overall OACs prescribed for patients with incident AF (5). Interestingly, regardless of the limited evidence in fragile patients, the usage of NOACs in CKD patients is still increasing (6). NOACs mainly depend on some degree of renal excretion (dabigatran 80%; edoxaban 50%; rivaroxaban 36%; apixaban 27%) (7). Thus, their pharmacokinetics properties may be effected by renal function impairment, and bring about consequent increase in free drug levels in the blood (8). Currently, there hasn't been any randomized clinical trials (RCTs) conducted yet, to assess the efficacy and safety of NOACs in AF patients with CKD. Nielsen *et al.* and Andò *et al.* assessed the efficacy and safety of NOACs across CKD subgroup, but only individual NOACs results were available for their study (9,10). Sardar *et al.* and Del-Carpio Munoz *et al.* reported a marked reduction of SSE and major bleeding of NOACs compared to that of warfarin in patients with CKD, but number of patients needed to treat (NNT) and net clinical benefit (NCB) was not detected (11,12). Of note, the concept of NCB has been developed and gradually used to quantify the balance between a reduced risk of SSE and an increased risk of bleeding with oral anticoagulants in AF during recent years (13). Whereas, evidence on NCB of AF was derived mainly from registry-based cohorts and observational studies, data from RCTs, especially for patients with CKD and AF is quite limited (14-16). Thus, we mainly evaluated the NCB property of NOACs in patients with AF and CKD by a pooled analysis and detect the difference of NCB on NOACs in varying degrees of renal function.

Methods

Data sources and search strategy

The study was performed according to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook (PROSPERO number: CRD42019116940). Medline, Embase, and Cochrane Library were searched from inception to Jan 25, 2019, for identifying all potential studies. For the subject term 'NOACs', the following terms were included: 'Pradaxa' OR 'dabigatran' OR 'Xarelto' OR 'rivaroxaban' OR 'Eliquis' OR 'apixaban' OR 'Savaysa' OR 'edoxaban' OR 'Bevyxxa' OR 'betrixaban' OR 'Non-vitamin K antagonist oral anticoagulants' OR 'direct oral anticoagulants' or 'NOACs' OR 'DOACs' OR 'new oral anticoagulants' OR 'factor Xa inhibitors' OR 'novel oral anticoagulants' OR 'factor II a inhibitors'. For the subject term 'atrial fibrillation', the terms were 'AF' OR 'atrial fibrillation'. For the subject term 'RCTs', the following terms were included: 'clinical trial' OR 'controlled clinical trial' OR 'randomized controlled trial'. The Boolean operator 'AND' was used to combine three search themes. Additionally, we identified unpublished trials from the ClinicalTrials.gov Website. The eligibility of each relevant study was independently assessed by two reviewers (Zhi-Chun Gu and Ling-Cong Kong), with any disagreements being disposed by a third author (Shuo-Fei Yang).

Study selection

The studies must met the following inclusion and exclusion criteria: (I) study were phase III RCTs of AF patients and taking NOACs in comparison to warfarin; (II) study reporting data about renal function and associated and detailed outcomes; (III) RCTs including patients with mitral stenosis or prosthetic cardiac valves, mean or median follow-up <6 months, <200 subjects, and NOAC phase II studies were excluded. If studies reporting over one publication, data were retrieved from the most complete publication, we also obtained the other reports for clarifying or complementing the information. Two reviewers (Zhi-Chun Gu and Ling-Cong Kong) independently evaluated study titles and abstracts to determine the eligibility, then full paper was obtained and evaluated the feasibility in line

with the inclusion criteria. A third author (Shuo-Fei Yang) resolved all discrepancies and uncertainties.

Study outcomes

Pre-specified outcomes for the current analysis were stroke and systemic embolism (SSE), major bleeding, all-cause death, and calculated NCB. The definition of major bleeding is followed by International Society of Thrombosis and Hemostasis (ISTH). All the data were classified as no CKD group (creatinine clearance-CrCl >80 mL/min), mild CKD (CrCl =50–80 mL/min), and moderate CKD (CrCl 30–50 mL/min), using the intention-to-treat principle. The CrCl was calculated by the Cockcroft-Gault formula.

Data extraction and quality evaluation, and bias assessment

Information were extracted by two reviewers independently using a priori designed form, including publication year, follow up duration, number of patients, mean age, sex, AF type, mean CHADS2 score, risk factors, and prior medicine use. In ARISTOTLE, moderate CKD was defined as CrCl 25–50 mL/min (17). The methodological quality of studies was assessed in line with the Cochrane Collaboration Risk of Bias Tool, which include random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases (18). When more than 10 studies were included, the visual inspection of funnel plots was used to explore potential publication bias (18).

Data analysis

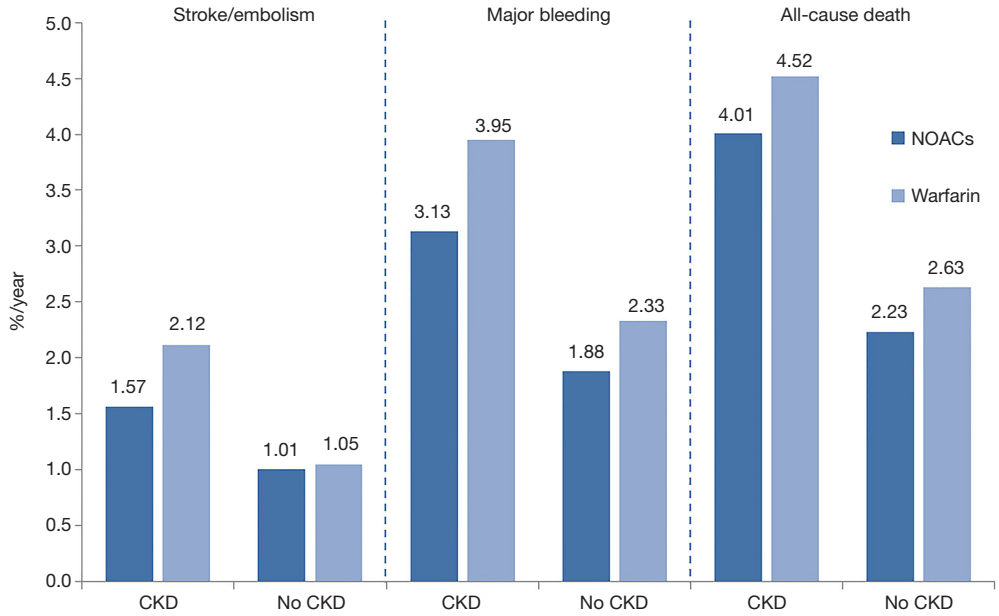
As mentioned above, subgroup data was abstracted as no CKD group, mild CKD group, and moderate CKD group, which did not provide combined data of CKD (CrCl <80 mL/min). Therefore, data of mild CKD group and moderate CKD group was combined as a one camp. In addition, 2 different dosages of NOACs (edoxaban 30 and 60 mg once daily in ENGAGE AF-TIMI 48, and dabigatran 110 and 150 mg twice daily in RE-LY) were in comparison with warfarin. Similarly, data of different dosages was merged as a one camp.

Relative risks (RRs) and 95% confidence intervals (CIs) of the outcomes in NOACs versus warfarin were calculated using a random-effects model. The heterogeneity was evaluated through I^2 test and Q statistic. P value of <0.05 at Q statistic indicated a significant heterogeneity, and I^2 of >50% represented considerable heterogeneity (19). The number of patients needed to treat (NNT) to prevent 1 event was calculated as: (1/absolute risk reduction) ×100, where absolute risk reduction was rate difference (event rates per 100 patients-year on warfarin minus event rates per 100 patients-year on NOACs) (14). Compared to warfarin, the NCB of NOACs was calculated following the formula: (rate of SSE on warfarin minus the rate of SSE on NOACs) – weight × (rate of major bleeding on NOACs minus rate of major bleeding on warfarin), where rate was event rates per 100 patients-year. We assigned the weighting factor of 1.5, and provided extra sensitivity analysis using 1.0 and 2.0 weighted factor (13). Because potential effect modifiers (demographic characteristics, risk factors, and prior medicine use) may lead to bias on outcomes of stroke/SE and major bleeding, a meta-regression analysis was performed to explore the outcomes influenced by these factors. Because original data of moderate CKD and mild CKD was combined as a one group, sensitivity analysis was performed in moderate CKD and mild CKD, respectively. Furthermore, additional analyses were performed to explore the influence by removing the low-dose arms (dabigatran 110 mg in RE-LY, and edoxaban 30 mg/15 mg in ENGAGE AF-TIMI 48). Meanwhile, interaction analysis was used for identifying the discrepancies in groups of different renal function. The statistical analyses were conducted by STATA software (version13, Statacorp, College Station, Texas, USA), P value <0.05 was considered statistically significant.

Results

Study summary

The flowchart of references was presented in *Figure S1*. We initially screened 3,244 records, with 842 duplicates. A total of 2,248 articles were excluded by reviewing the titles and abstracts. The remained 154 full texts were obtained, 46 texts met the inclusion criteria, but only 6 studies provided the original data. J-ROCKET AF was excluded from the analysis due to the limited population representation (only Japanese). Due to the use of aspirin, not warfarin, as a comparison, we excluded the AVERROES study from the analysis. Eventually, four phase III trials, comparing NOACs to warfarin in AF patients, were included in the current analyses: the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial, comparing dabigatran with warfarin (20); the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin



Total (n)	45,265	25,687	45,319	25,706	22,711	13,362
NOACs events (n)	881	340	1,595	525	1,140	339
Warfarin events (n)	766	235	1,326	457	859	292

Figure 1 Pooled rates of outcomes in patients with and without CKD. Rate is expressed as %/year. NOACs, non-vitamin K antagonist oral anticoagulants; CKD, chronic kidney disease.

K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, comparing rivaroxaban to warfarin (21); ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, comparing apixaban to warfarin (17); ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) trial, comparing edoxaban to warfarin (22).

As shown in *Figure 1*, 70,952 patients were included in the analyses, 45,265 with CKD, of whom 26,770 were treated with NOACs and 18,495 with warfarin, while 25,687 without CKD, of whom 15,172 treated with NOACs and 10,515 with warfarin. A total of 881 SSEs (1.57%/year) in NOACs-treated patients with CKD and 340 SSEs (1.01%/year) in NOACs-treated patients without CKD were reported. Similarly, 1,595 major bleedings (3.13%/year) in NOACs-treated patients with CKD and 525 major bleedings (1.88%/year) in NOACs-treated patients without CKD were reported. Characteristics of subjects with CKD were shown in *Table 1*. The duration of median follow-up ranged from 1.5 to 2.8 years across four trials. Except for the RE-LY, which was not double-blinded, all trials met the needs of bias tool items. The included studies had low bias overall and thus had high quality for our investigation (*Table S1*).

NOACs versus warfarin in patients with CKD and without CKD

In patients with CKD, NOACs demonstrated a significantly decreased risk for SSE by 20% (RR: 0.80, 95% CI: 0.73–0.88, P<0.01, I^2: 0.0%), major bleeding by 21% (RR: 0.79, 95% CI: 0.66–0.96, P=0.017, I^2: 85.3%), and all-cause death by 9% (RR: 0.91, 95% CI: 0.84–0.99, P=0.031, I^2: 0.0%) when compared with warfarin (*Figure 2A*). However, in patients without CKD, SSE risk did not significantly differ in patients treated with NOACs and warfarin (RR: 0.99, 95% CI: 0.75–1.32, P=0.96, I^2: 64.8%). The risks of major bleeding (RR: 0.80, 95% CI: 0.58–1.09, P=0.15, I^2: 84.2%) and all-cause death (RR: 0.87, 95% CI: 0.74–1.01, P=0.07, I^2: 0.0%) were numerically lower in NOACs arm, but showed no statistical significance (*Figure 2B*). No differences in treatment effect

Table 1 Baseline characteristics of included trials by CKD

Characteristic	RE-LY (dabigatran)			ROCKET AF (rivaroxaban)		ARISTOTLE (apixaban)			ENGAGE AF (edoxaban)		
	No CKD	Mild CKD	Moderate CKD	No or mild CKD	Mild CKD	No CKD	Mild CKD	Moderate CKD	No CKD	Mild CKD	Moderate CKD
Year		2013		2011			2012			2016	
Follow-up, years		2.0		1.9			1.5			2.8	
CrCL (mL/min)	>80	50–80	30–50	>50	30–50	>80	50–80	25–50	>95	50–95	30–50
Dose of NOACs, mg	110/150	110/150	110/150	20	15	5	5	2.5*	60/30	60/30	30/15
Number	5,844	8,553	3,554	11,205	2,949	7,518	7,587	3,017	7,818	9,049	3,858
Age, years	68	72	76	71	79	63	72	78	61	73	79
Female, %	30	36	47	35	55	26	37	53	24	38	54
Type of AF, %											
Paroxysmal	33	31	33	18	16	16	15	13	NA	NA	NA
Persistent or permanent	67	69	67	80	82	84	85	87	NA	NA	NA
$CHADS_2$, mean	NA	NA	NA	3.4	3.7	1.9	2.2	2.6	2.6	2.9	3.1
Risk factors, %											
CHF	29	25	33	62	65	31	30	33	65	56	55
Hypertension	73	79	86	90	92	90	86	85	96	93	92
Diabetes	23	22	29	42	32	29	23	21	47	35	28
Prior stroke or TIA	22	19	20	56	50	15	22	25	22	30	30
Prior MI	NA	NA	NA	17	19	13	15	17	NA	NA	NA
Prior aspirin use	39	39	42	36	36	30	31	32	29	29	31
Prior VKA use	64	66	65	62	62	42	43	46	60	59	58

*, apixaban 2.5 mg twice daily is used for patients with serum creatinine >1.5 mg/dL. AF, atrial fibrillation; CKD, chronic kidney disease; CHF, congestive heart failure; CrCL, creatinine clearance; MI, myocardial infarction; NA, not available; TIA, transient ischemic attack; VKA, vitamin K antagonist; RE-LY, randomized evaluation of long-term anticoagulation therapy; 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; ARISTOTLE, apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; ENGAGE AF, effective anticoagulation with factor Xa next generation in atrial fibrillation.

were found between CKD and no CKD arms on SSE ($P_{interaction}$=0.206), major bleeding ($P_{interaction}$=0.947), and all-cause death ($P_{interaction}$=0.612) (*Figure S2*).

NNT and NCB of NOACs in patients with CKD and without CKD

In patients with CKD, the event rates per 100 patients-year of SSE were 1.57 for NOACs, and 2.12 for warfarin, which was translated to NNT of 182, indicating that 182 NOACs patients could prevent 1 SSE event per year than warfarin patients (*Table 2*). Similarly, the NNT of major bleeding was 122, and the NNT of all-cause death was 196. In patients without CKD, all the NNTs of outcome were positive (2,500 for SSE, 222 for major bleeding, and 250 for all-cause death, respectively). Thus, the overall beneficial effect of NOACs compared with warfarin to prevent 1 SSE, major bleeding, or all-cause death would be greater in patients with CKD than those without CKD, with a smaller NNT. The NCB analyses stratified by CKD were presented

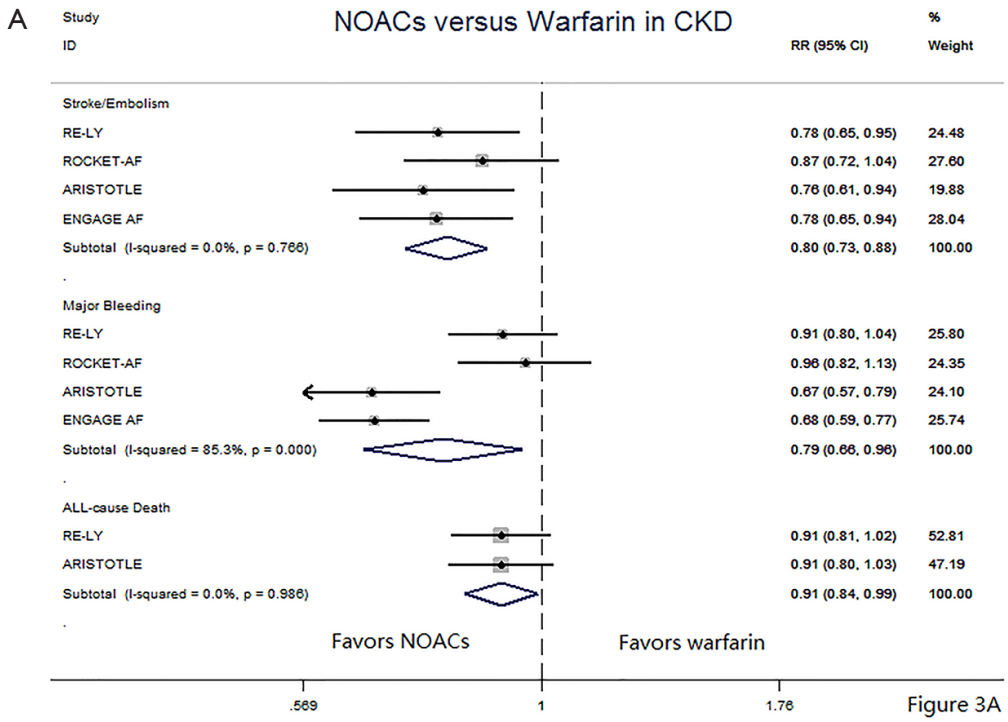


Figure 3A

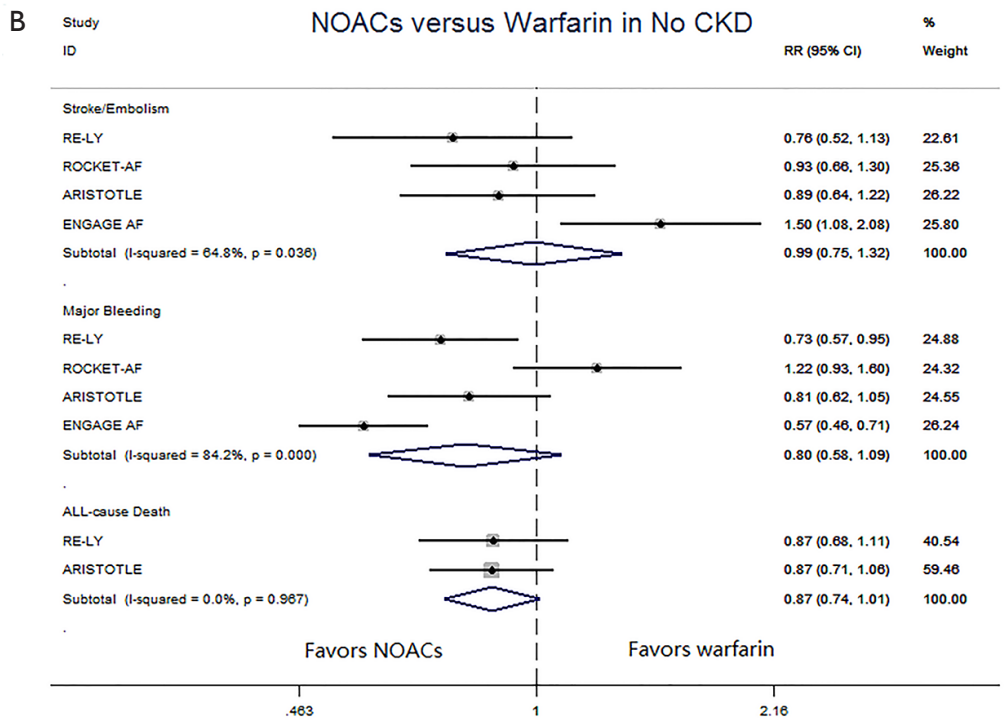


Figure 2 Outcomes of NOACs versus warfarin in patients with (A) and without CKD (B). NOACs, non-vitamin K antagonist oral anticoagulants; CKD, chronic kidney disease; RR, relative risk; 95% CI, 95% confidence interval.

Table 2 Event rates and number needed to treat of NOAC versus Warfarin

Outcome	NOAC (%/year)	Warfarin (%/year)	ARR	NNT
Stroke/embolism				
Moderate CKD	2.13	2.66	0.53	189
Mild CKD	1.39	1.96	0.57	175
CKD	1.57	2.12	0.55	182
No CKD	1.01	1.05	0.04	2500
Major bleeding				
Moderate CKD	3.92	5.39	1.47	68
Mild CKD	2.88	3.56	0.68	147
CKD	3.13	3.95	0.82	122
No CKD	1.88	2.33	0.45	222
All-cause death				
Moderate CKD	7.13	7.86	0.73	137
Mild CKD	3.36	3.91	0.55	182
CKD	4.01	4.52	0.51	196
No CKD	2.23	2.63	0.40	250

ARR, absolute rate reduction; CKD, chronic kidney disease; NOAC, novel oral anticoagulant; NNT, number needed to treat; %/year, events per 100 patients-years.

in *Figure 3*. When using a weighted factor of 1.5, NOACs had a positive NCB in patients with CKD when compared with warfarin, yielding an NCB of 1.78 (95% CI: 1.29–2.27, P<0.01). Similarly, in patients without CKD, NOACs had superior NCB value than warfarin (NCB: 0.72, 95% CI: 0.22–1.22, P<0.01). Interestingly, there was an incremental NCB with the deterioration of renal function (0.72 for no CKD, 1.59 for mild CKD, 2.74 for moderate CKD, and $P_{interaction}$=0.001 among different renal function). Results of sensitivity analyses, using weighted factor of 1.0 and 2.0, were consistent with those of the primacy analyses.

Sensitivity analysis

The meta-regression analysis indicated that no potential confounding was present (*Table S2*). When we performed the sensitivity analysis in various degrees of renal function, the results were confirmed in the mild CKD group comparing NOACs with warfarin (*Figure S3*). In the moderate CKD group, NOACs tended to significantly reduce the risk of SSE (RR: 0.85, 95% CI: 0.72–1.00, P=0.05) and major bleeding (RR: 0.74, 95% CI: 0.53–1.03, P=0.08) compared to warfarin (*Figure S4*). After excluding low-dose results of RE-LY and ENGAGE AF-TIMI 48 trials in this analysis, the results were similar with the

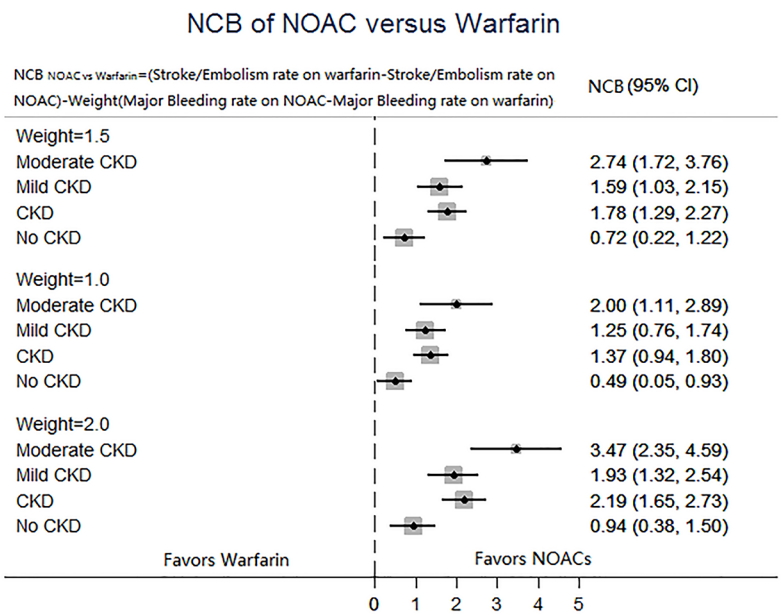


Figure 3 NCB of NOACs versus warfarin in patients with CKD and without CKD. NCB, net clinical benefit; NOACs, non-vitamin K antagonist oral anticoagulants; CKD, chronic kidney disease; 95% CI, 95% confidence interval.

primacy analyses (*Figures S5*,*S6*).

Publication bias

We did not perform Funnel plot as the limited number of eligible trails (four RCTs).

Discussion

CKD has been related with higher risk for thromboembolic and bleeding occurrence, and combination of CKD and AF confers significantly greater risks (2,3). NOACs provide a better efficacy and safety profile when compared with warfarin in general population. However, compared with warfarin, the NCB property of NOACs for these AF and CKD patients is limited. Because of this reason, we have assessed the efficacy, safety, and NCB of NOACs in patients with AF and CKD, and have obtained the following main results. Firstly, NOACs significantly reduced the risk for SSE, major bleeding and all-cause death in patients with CKD when compared to warfarin. More importantly, NOACs, compared with warfarin, could bring about a progressively increased NCB value with the deterioration of renal function.

Outcomes of NOACs in patients with AF and CKD

Although CKD is not a component factor of the CHADS2 score or CHA2DS2-VASC score, it is closely associated with their risk factors, such as congestive heart failure, hypertension, age, diabetes, and prior stroke or transient ischemic attack (23). Warfarin is widely administered in AF and CKD patients due to its low-cost and availability of reversal agents. However, it is important to recognize that CKD is associated with a suboptimal TTR in AF patients treated with warfarin (3). Inadequate control of TTR might contribute to increased risk of thromboembolism as well as bleeding (24). Similarly, our results found that CKD patients receiving NOACs also brought more SSE events (1.57%/year versus 1.01%/year) and major bleeding (3.13%/year versus 1.88%/year) than no-CKD patients, meaning that CKD is still a strong factor for thromboembolism and hemorrhage despite the use of NOACs. CKD progression is often characterized by fluctuant creatinine levels and acute kidney injury events that may affect renal elimination of NOACs and make patients exposed at an increased risk of hemorrhage (25). Hence, intensive caution should be proceeded with NOACs in CKD patients, including close monitoring of renal function.

Outcomes of NOACs versus warfarin in CKD patients

All the sub-analysis of included trials divided the CKD into 3 different levels based on CrCl (>80 mL/min, 50 to 80 mL/min, and <50 mL/min). In RE-LY, dabigatran 150 mg twice daily showed a significantly decreased risk for SSE in mild and moderate CKD, and 110 mg significantly decreased the risk for major bleeding only in patients with moderate CKD. No difference was reported between CKD and no CKD subgroup (20). In ROCKET AF, rivaroxaban 15 mg daily in subjects with moderate CKD, did not show significant difference in comparison to warfarin regarding the SSE and major bleeding (21). In ARISTOTLE, apixaban 5 mg twice daily was more effective than warfarin at preventing SSE and major bleeding in mild CKD (17). In ENGAGE AF-TIMI 48, edoxaban 60 mg daily was associated with fewer SSE events in mild CKD as well as fewer major bleeding events in moderate CKD (22). Our analysis, merging all the NOACs for powerful statistics, showed that the use of NOACs was superior to warfarin for the prevention of SSE and major bleeding in CKD patients. In addition, when the low-dose arms of RE-LY and ENGAGE AF-TIMI 48 were excluded in the analysis, the results were similar. Thus, NOACs represent a preferable and valuable alternative to warfarin in this clinical setting, while these advantages were not detected in patients without CKD.

NCB of NOACs versus warfarin in patients with CKD

NCB, which incorporates both the risk for SSE and major bleeding, provides a more quantitatively informed basis for the decision-making on the optimal anticoagulant therapy in AF patients. Our analysis showed a superior NCB property of NOACs in comparison to warfarin in patients with AF and CKD. Actually, patients receiving NOACs could prevent the event in around 1.8 per 100 patients with CKD. Similarly, the use of NOACs would avoid the event in around 0.7 per 100 patients without CKD. Interestingly, our analysis found that NCB was progressively increased with the deterioration of renal function ($P_{interaction}$=0.001), with the greatest NCB of 2.74 in moderate CKD patients. In the fragile population, the major contributor of these results is a significant lower event rate of major bleeding in the NOACs group versus warfarin group, yielding a rate difference of 1.47. In fact, renal dysfunction is regarded as

component factor of HAS-BLED, the most popular score currently used for the assessment of bleeding risk (26). Additionally, using impact weights of 1.0 and 2.0 for the difference in rates of major bleeding between patients taking NOACs or warfarin did not change our estimate of NCB. Thus, based on our analysis of NCB, NOACs is preferable to warfarin for all those with AF, and the effect is markedly greater in patients with CKD.

Study limitations

Several limitations are worth mentioning. Firstly, the included studies were not especially assigned to assess the efficacy and safety of NOACs in CKD patients. And further analysis for patient-level data associated with patient demographics, bleeding risk factors, concomitant drugs etc. were not obtained. However, we performed a meta-regression analysis to assess available potential effect modifiers in baseline characteristics, and the results failed to detect any observational confounding factor as having influenced the primacy outcome. In addition, Singer's method was used to calculate the NCB in our analysis using a weighted index of 1.5, which cannot account for all clinical variables (13). However, we performed a sensitivity analysis using weighted factor of 1.0 and 2.0, and a similar result was obtained. In fact, currently, there are no methods available to estimate the NCB perfectly. Finally, the J-ROCKET trial, which was a phase III trial comparing rivaroxaban with warfarin, was not included in the analysis due to the small sample size and enrolling patients only in one country, leading to the possible selection bias in our analysis (27). It is important to acknowledge that our results only involve limited number of studies and therefore cannot be extrapolated to the overall population with AF and CKD, while may be used only in patients with similar characteristics included in the present analysis.

Conclusions

The use of NOACs may bring about a better profile on efficacy, safety, and NCB when compared to warfarin in CKD patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

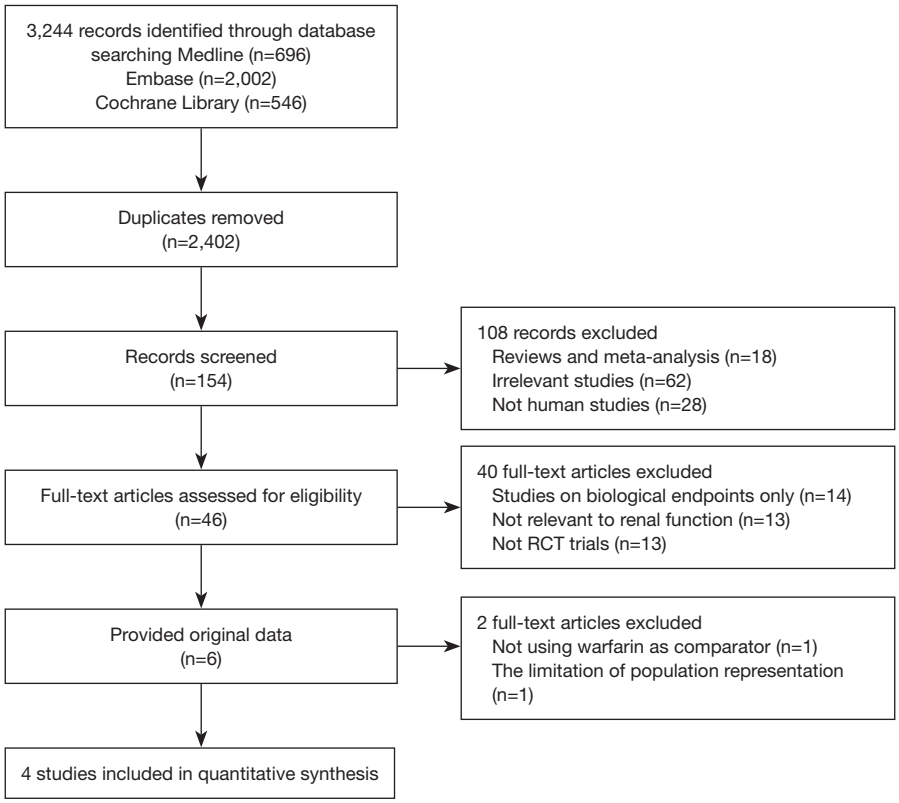

Figure S1 Flow diagram for the selection of eligible randomized controlled trials.

Table S1 Quality assessment of included trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary risk
RE-LY (20)	L	L	H	L	L	L	L	L
ROCKET AF (21)	L	L	L	L	L	U	L	L
ARISTOTLE (17)	L	L	L	L	L	U	L	L
ENGAGE AF-TIMI 48 (22)	L	L	L	L	L	L	L	L

L, low risk; U, unclear risk; H, high risk.

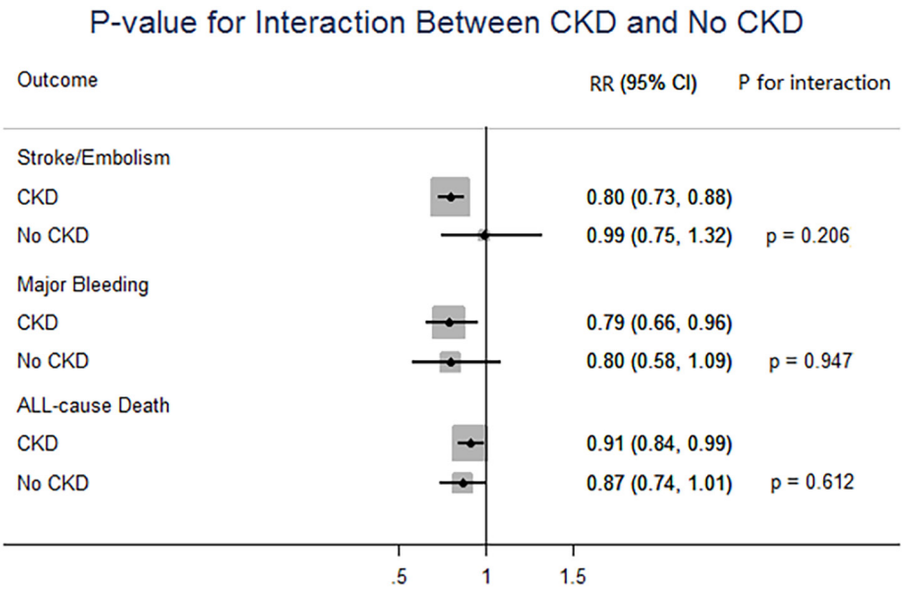

Figure S2 P value for interaction between patients with and without CKD. CKD, chronic kidney disease.

Table S2 Meta-regression analysis

Variable	Stroke/embolism (P value/tau^2)	Major bleeding (P value/tau^2)
All cohort		
Age	0.777/0.026	0.114/0.010
Female	0.608/0.017	0.214/0.021
CHF	0.260/0.000	0.871/0.060
Hypertension	0.270/0.000	0.621/0.052
Diabetes	0.261/0.000	0.856/0.060
Stroke or TIA	0.528/0.001	0.326/0.031
Aspirin	0.430/0.000	0.200/0.019
VKA	0.759/0.020	0.476/0.043
CKD		
Age	0.937/0.000	0.670/0.019
Female	0.988/0.000	0.332/0.006
CHF	0.912/0.000	0.792/0.046
Hypertension	0.953/0.000	0.597/0.046
Diabetes	0.860/0.000	0.894/0.031
Stroke or TIA	0.866/0.000	0.941/0.027
Aspirin	0.926/0.000	0.172/0.006
VKA	0.844/0.000	0.477/0.021
No CKD		
Age	0.365/0.058	0.637/0.018
Female	0.331/0.072	0.602/0.006
CHF	0.216/0.029	0.290/0.134
Hypertension	0.382/0.020	0.654/0.134
Diabetes	0.214/0.000	0.306/0.133
Stroke or TIA	0.789/0.098	0.493/0.038
Aspirin	0.486/0.036	0.762/0.102
VKA	0.898/0.097	0.606/0.134

P values: it is the results of meta-regression for the relationship between each variable and the outcomes; CHF, congestive heart failure; TIA, transient ischemic attack; VKA, vitamin K antagonist.

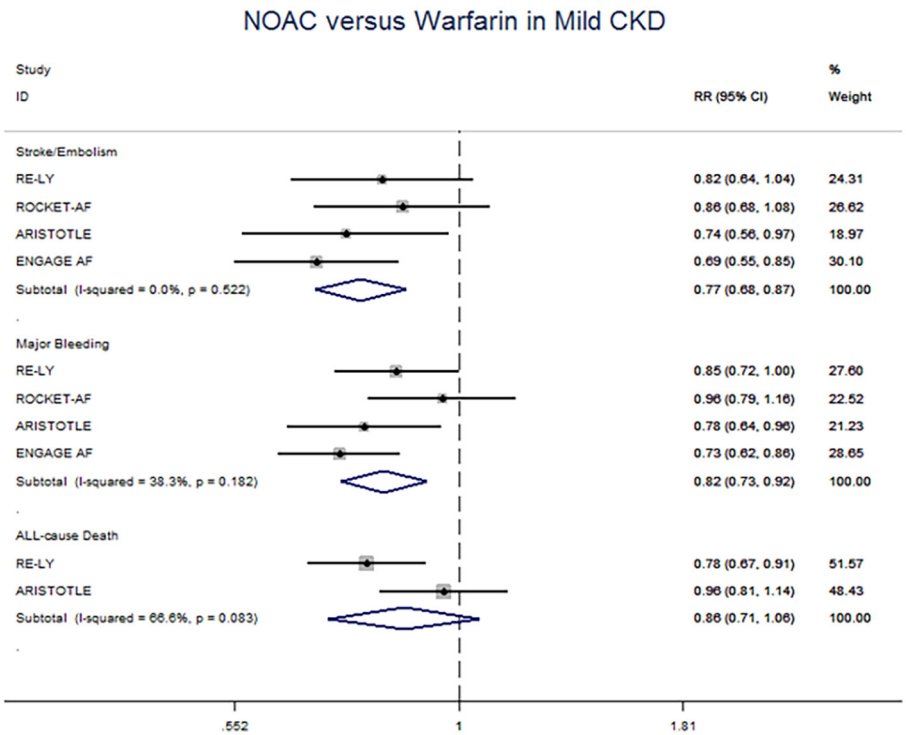

Figure S3 Sensitivity analysis of NOAC versus warfarin in mild CKD. NOAC, non-vitamin K antagonist oral anticoagulant; CKD, chronic kidney disease.

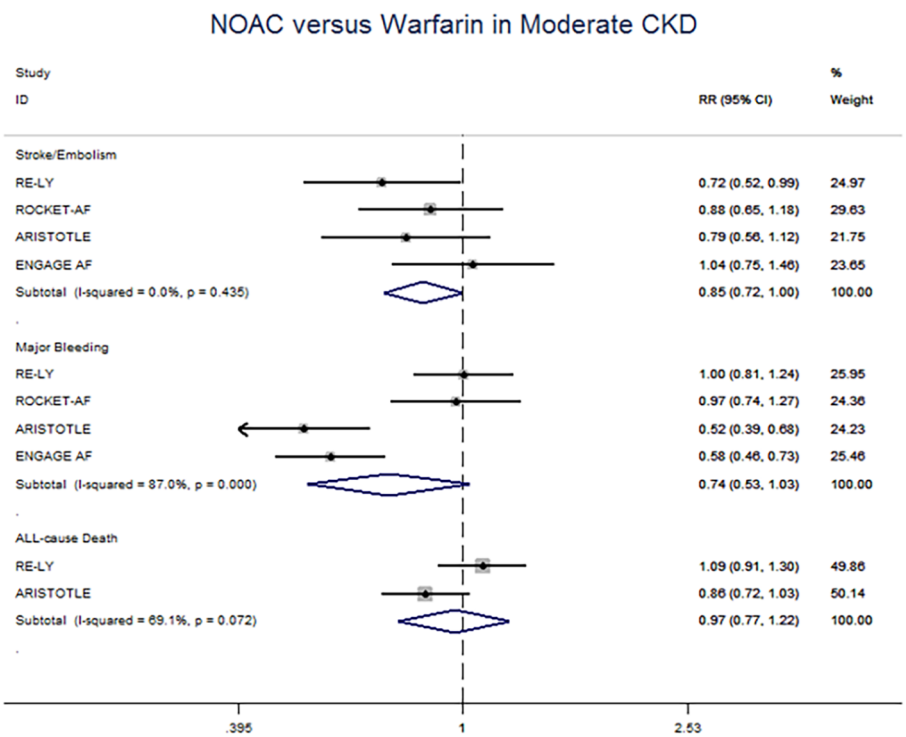

Figure S4 Sensitivity analysis of NOAC versus warfarin in moderate CKD. NOAC, non-vitamin K antagonist oral anticoagulant; CKD, chronic kidney disease.

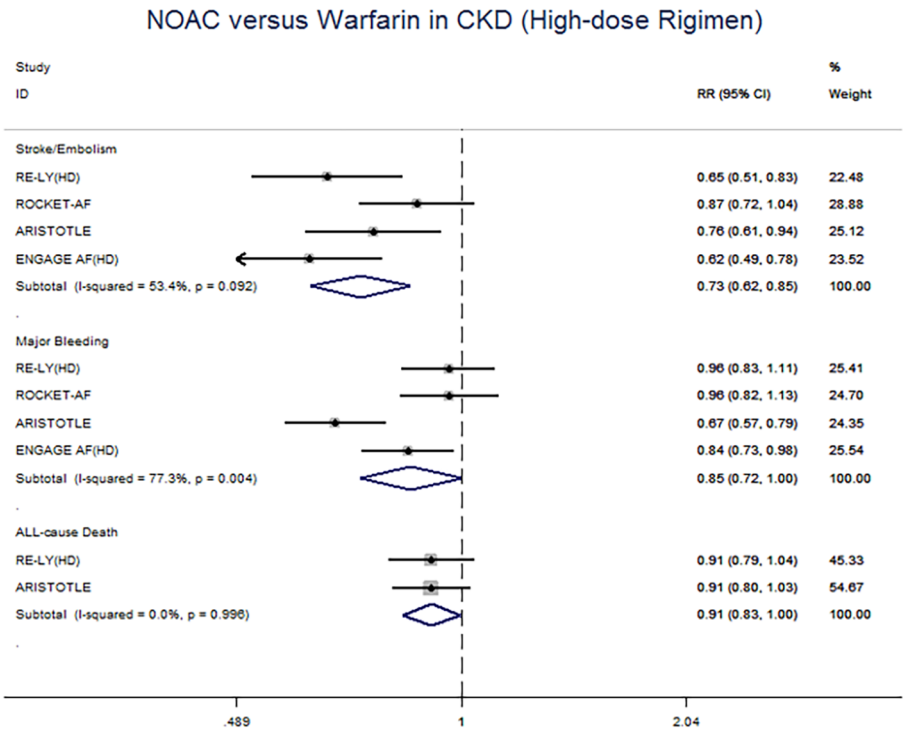

Figure S5 Sensitivity analysis of NOAC versus warfarin in CKD after removing the low-dose regimen. NOAC, non-vitamin K antagonist oral anticoagulant; CKD, chronic kidney disease.

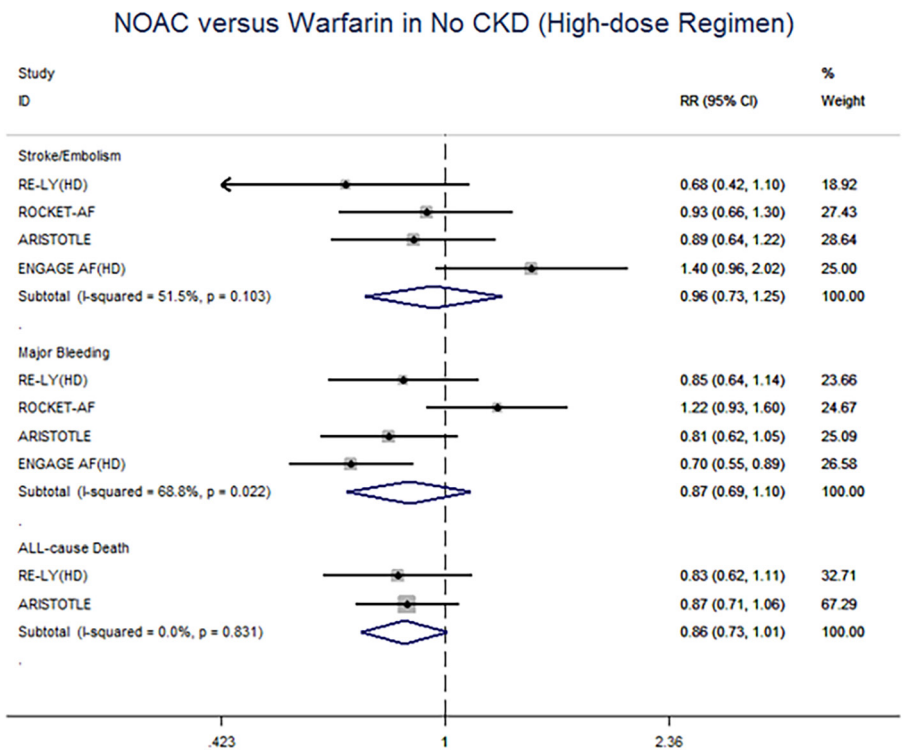

Figure S6 Sensitivity analysis of NOAC versus warfarin in no CKD after removing the low-dose regimen. NOAC, non-vitamin K antagonist oral anticoagulant; CKD, chronic kidney disease.