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Review Article

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

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ABSTRACT

Background: Patients with warfarin have a potential risk of warfarin-related nephropathy, which could result in the discontinuation of anticoagulation therapy. The question of whether non-vitamin K antagonist oral anticoagulants (NOACs) use is associated with increased risk of renal impairment in atrial fibrillation (AF) patients remains unanswered.
Methods: Studies were systematically searched through Medline, Embase, Cochrane Library databases, and ClinicalTrials.gov Website. Randomized controlled trials (RCTs) reporting renal impairment events and observational nationwide database studies presenting adjusted hazard ratio (HR) in AF patients with NOACs were identified. The Primacy outcome was renal impairment, defined as a composite of any renal disorder. The secondary outcomes were narrow definition of renal failure (including renal failure, acute renal failure, chronic renal failure, acute prerenal failure and postrenal failure) and individual renal impairment reported in involved studies. HR and 95% confidence intervals (95%CI) were calculated using fixed- or random-effects models according to the extent of heterogeneity. Subgroup analyses were conducted according to individual NOACs, study types and different controls.
Results: Totally, 189,483 patients from 11 RCTs and 3 observational database studies were included in the analysis (119,188 patients with NOACs and 70,295 patients with vitamin K Antagonists or acetylsalicylic acid). Overall results indicated a significantly lower risk of renal impairment in AF patients with NOACs versus VKAs/acetylsalicylic acid (HR: 0.67, 95%CI: 0.62–0.73). Results of narrow definition of renal impairment were accordant with the primacy outcome (HR: 0.65, 95%CI: 0.60–0.71). Compared with VKAs or acetylsalicylic acid, dabigatran (HR: 0.64, 95%CI: 0.56–0.72), rivaroxaban (HR: 0.66, 95%CI: 0.55–0.77) and apixaban (HR: 0.73, 95%CI: 0.59–0.87) were all associated with a significantly lower risk of renal impairment, with the exception of edoxaban (HR: 0.79, 95%CI: 0.30–1.27).
Conclusions: Patients with NOACs might bring about a lower risk of renal impairment compared to VKA or acetylsalicylic acid. Further specialized designs of RCTs and real-world studies on evaluation of renal function are warranted to obtain a robust result on this issue.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia with a world-wide prevalence of 2–3% [1]. The most feared complication of AF is stroke, and AF increases the risk of stroke by about five-fold. Over 80% of ischemic stroke of cardioembolic type are AF related, suggesting a strong association between AF and stroke [2]. Accordingly, stroke prevention therapy, mainly oral anticoagulation, is the principal priority in the management of AF [3]. Vitamin K antagonists (VKAs), chiefly warfarin, being commonly used for anticoagulation for > 60 years, could decrease the risk of thromboembolic events and all-cause mortality in AF patients [4]. Nevertheless, some warfarin-treated

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patients suffered an accelerated progression of chronic kidney disease (CKD) and acute kidney injury (AKI), which was recently recognized as warfarin-related nephropathy, resulting in the discontinuation of anticoagulation therapy [5,6]. Non-vitamin K antagonist oral anticoagulants (including dabigatran, rivaroxaban, apixaban, and edoxaban), are now increasingly used for the prevention of stroke and systemic embolism in AF patients, with therapeutically advantageous over or at least non-inferior in terms of thromboprophylaxis, and lower intracranial hemorrhage and micro-hemorrhage rates in comparison to warfarin [7–9]. NOACs have varying degrees of renal excretion, from the highest 80% for dabigatran to 50%, 33% and 27% for edoxaban, rivaroxaban and apixaban, respectively [10]. However, the potential renal toxicity of NOACs in AF patients remains unanswered. Some cases reported the anticoagulated-related nephropathy linked to NOACs [11,12], while post hoc analyses of randomized controlled trials (RCTs) found better preservation of renal function of NOACs in AF patients when compared with warfarin [13]. One meta-analysis involving 10 RCTs indicated that NOACs had similar risk of renal failure compared with VKAs/low-molecular weight heparin (LMWH) [14]. However, the insufficient sample size in RCTs, wide range of indications (including AF, venous thromboembolism, and hip/knee arthroplasty), and the combinated controls of VKAs and LMWH might result in an underestimated or overestimated risk of renal failure. It is noteworthy that some high-quality real-world studies focusing on the risk of renal impairment in anticoagulated patients with AF have been published recently, and more valuable information based on large populations was available to make the conclusion on this issue. The present study is to summarize current evidences including available RCTs and well-designed real-world studies to conduct a pooled analysis with regards to the risk of renal impairment in AF patients receiving NOACs.

2. Methods

2.1. Data sources and searches

The present study was performed according to the standards of the Cochrane Handbook and the PRISMA Statement for Reporting Systemic Reviews and was conducted based on priori established protocol (PROSPERO: CRD42018108367) [15–17]. We electronically searched the databases of Medline, Embase, and Cochrane Library to identify all potentially eligible studies from inception to Jul 31st, 2018 with the following searching strategy: “Non-vitamin K antagonist oral anticoagulants” or “NOACs” or “direct oral anticoagulants” or “DOACs” or “novel oral anticoagulants” or “new oral anticoagulants” or “factor Xa inhibitors” or “factor IIa inhibitors” or “dabigatran” or “Pradaxa” or “rivaroxaban” or “Xarelto” or “apixaban” or “Eliquis” or “edoxaban” or “Savaysa” or “betrixaban” or “Bevyxxa” in combination with “atrial fibrillation” or “AF”. Moreover, unpublished data were sought from the ClinicalTrials.gov website. References of identified records were scrutinized manually to find any potentially eligible articles. Databases searching was conducted independently by two reviewers (Chi Zhang and Zhi-Chun Gu), and disagreements were resolved by discussion with other authors (Ying-Li Zheng and Hou-Wen Lin).

2.2. Study selection and outcomes

To be eligible for inclusion, studies had to be RCTs or observational studies concerning NOACs that reported renal outcome. The eligible observational studies should be high-quality nationwide or health insurance database studies presenting adjusted or matched results. Studies in form of abstract, reported unmatched or unadjusted results, or without baseline data were excluded. Primacy outcome was renal impairment, defined as a composite of any renal disorder. Since renal impairment could be described in various forms in different studies, the following outcomes were used as renal impairment, which included renal failure, acute renal failure, chronic renal failure, renal impairment, nephritis, nephropathy, nephrotic syndrome, acute prerenal failure and postrenal failure, renal disorder, renal injury, renal tubular necrosis, ≥30% decline in eGFR and doubling of the serum creatinine level. The secondary outcomes were narrow definition of renal failure (including renal failure, acute renal failure, chronic renal failure, acute prerenal failure and postrenal failure) and individual renal impairment reported in the study. Two reviewers (Chi Zhang and Zhi-Chun Gu) assessed all study titles and abstracts independently to determine eligibility, and entire papers were reviewed and assessed based on inclusion criteria. All discrepancies were resolved by consulting other investigators (Ying-Li Zheng and Hou-Wen Lin).

2.3. Data extraction, quality evaluation and bias assessment

Two reviewers (Chi Zhang and Zhi-Chun Gu) independently performed the data extraction based on the standard data extraction form, containing study characteristics, patient demographics, clinical characteristics, and data of reported renal outcome. Renal function data of RCTs that was not reported in the original publications was extracted from the ClinicalTrials.gov website.

The quality of included RCTs was assessed according to the Cochrane Collaboration Risk of Bias Tool [18,19]. The risk of bias of observational studies was evaluated with the following domains: apply of adjusted method to handle with selection bias; the presence of residual confounding; apply of methods to deal with covariates related to time-varying and information; detailed reporting of baseline characteristics and f measures [20]. Potential publication bias was explored using Begg's test [21].

2.4. Data analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) of various forms of renal impairment, were calculated for each study. Pooled analyses were evaluated using fixed-effect models or random-effects models according to the extent of heterogeneity. To obtain a composite outcome, individual renal impairment data was merged. Corresponding HRs and CIs were firstly calculated for included RCTs, and thereafter adjusted HRs and 95%CI of included observational studies were pooled. Heterogeneity was assessed with I^2 test and χ^2-based Q test. I^2 values of > 50% represented considerable heterogeneity, and a cutoff value of $p < 0.1$ suggested significant heterogeneity [22]. Subgroup analyses were conducted according to individual NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban), study types (RCTs and database studies), and control drugs (VKAs or acetylsalicylic acid). Meta-regression analysis was carried out to investigate demographic characteristics of the included studies. Sensitivity analyses were performed by excluding each study in turn, to address the relative importance of individual studies. Moreover, further analyses were conducted to assess the effect by excluding studies that involved ablation, cardioversion, PCI, acetylsalicylic acid as control, low dosage arms of NOACs, or follow-up < 3 months. Statistical analyses were performed with the use of STATA software (version13, Statacorp, College Station, Texas, USA), and p value of < 0.05 was statistically significant difference.

3. Results

3.1. Study evaluation

The results of the electronic search and article selection were shown in Fig. S1, and the reasons for excluded RCTs and database studies were presented in Table S1-S2. Our final analysis included 11 RCTs and 3 observational studies [13,23–34]. A total of 189,483 patients were enrolled, including 119,188 patients with NOACs and 70,295 patients with vitamin K Antagonists (VKAs) or acetylsalicylic acid. The characteristics of the 11 RCTs were displayed in Table 1. Publication periods was from 2009 to 2018, with the up-to-date EMANATE study [28] and

Table 1
Characteristics of 11 included randomized trials.

Study (year)	NCT number	Intervention with dosage	Patients (number)	Comparison	Patients (number)	Follow up (year)	Reported renal impairment
RE-LY 2009	NCT00262600	Dabigatran 110 mg twice	5983	Warfarin	5998	2.0	Renal Failure, Acute Renal Failure, Chronic Renal Failure, Renal Impairment, Nephritis, Nephropathy, Nephrotic Syndrome, Acute Prerenal Failure, Renal disorder, Renal injury, Renal tubular necrosis
		Dabigatran 150 mg twice	6059				
ROCKET-AF 2011	NCT00403767	Rivaroxaban 20 mg once	7111	Warfarin	7125	1.9	Renal Failure, Acute Renal Failure, Chronic Renal Failure, Renal Impairment, Nephritis, Nephrotic Syndrome, Nephropathy, Acute Prerenal Failure
ARISTOTLE 2011	NCT00412984	Apixaban 5 mg twice	9088	Warfarin	9052	1.8	Renal Failure, Acute Renal Failure, Chronic Renal Failure, Renal Impairment, Nephrotic Syndrome, Postrenal failure, Renal injury, Renal tubular necrosis
AVERROES 2011	NCT00496769	Apixaban 5 mg twice	2807	Acetylsalicylic acid 81–324 mg	2791	1.1	Renal Failure, Acute Renal Failure, Chronic Renal Failure, Renal Impairment
J-ROCKET AF 2011	NCT00494871	Rivaroxaban 15 mg once	639	Warfarin	639	2.5	Renal Failure, Acute Renal Failure, Renal Impairment, Acute Prerenal Failure
ENGAGE AF-TIMI48 2013	NCT00781391	Edoxaban 60 mg once	7002	Warfarin	7012	2.8	Renal Failure, Acute Renal Failure, Chronic Renal Failure, Renal Impairment, Nephrotic Syndrome, Nephropathy, Acute Prerenal Failure, Renal injury, Renal tubular necrosis
		Edoxaban 30 mg once	7002				
X-VERT 2014	NCT01674647	Rivaroxaban 20 mg once	988	Vitamin K Antagonist	499	0.08	Acute Renal Failure,
PIONEER AF-PCI 2016	NCT01830543	Rivaroxaban 15 mg once	696	Vitamin K Antagonist	697	1.0	Renal Failure, Acute Renal Failure, Renal Impairment, Acute Prerenal Failure,
		Rivaroxaban 2.5 mg twice	706	Vitamin K Antagonist			
RE-CIRCUIT 2018	NCT02348723	Apixaban 5 mg twice	338	Warfarin	338	0.15	Acute Renal Failure, Renal Impairment
EMANATE 2018	NCT02100228	Apixaban 5 mg twice	735	Vitamin K Antagonist	721	0.08	Acute Renal Failure, Postrenal failure
Yamashita 2012	NCT00829933	Edoxaban 60 mg once	131	Warfarin	129	0.12	Nephrotic Syndrome
		Edoxaban 45 mg once	134				
		Edoxaban 30 mg once	131				

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; AVERROES: A Phase III Study of Apixaban in Patients With Atrial Fibrillation; ENGAGE AF-TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; X-VERT: eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion; PIONEER AF-PCI 2016: A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-CIRCUIT: Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy; EMANATE: Eliquis evaluated in acute cardioversion coMpared to usuAl treatmeNts for AnticoagulaTion in subjEcts with atrial fibrillation.

Table 2
Characteristics of 3 included database studies.

Study (year)	Country or region	Data source	Inclusion period	Intervention	Patients (number)	Comparison	Patients (number)	Adjusted method	Adjusted variables	Follow up
Yi-Hsin Chan 2016	Taiwan	Taiwan National Healthy Insurance Registry Database (NHIRD)	2012.6.1–2013.12.31	Dabigatran	9958	Warfarin	9974	IPTW	(1)	0.69 years for dabigatran users; 0.71 years for warfarin users.
Xiaoxi Yao 2017	U.S.A.	OptumLabs Data Warehouse	2010.10.1–2016.4.30	NOACs (Dabigatran, rivaroxaban, apixaban)	5584	Warfarin	4185	IPTW	(2)	10.7 ± 9.9 months
Yi-Hsin Chan 2018	Taiwan	Taiwan National Healty Insurance Registry Database (NHIRD)	2012.6.1–2016.12.31	NOACs (Dabigatran, rivaroxaban, apixaban)	54,086	Warfarin	21,135	IPTW	(3)	NR

NOACs: Non-vitamin K Antagonist Oral Anticoagulants; IPTW: inverse probability of treatment weights of propensity scores; U.S.A.: United States of America; NR: not reported; (1): Adjusted variables including age, comorbidities, previous bleeding history, and medication history, such as use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aminoglycoside, and steroids at baseline;(2): Adjusted variables including the demographics, comorbidities, and baseline medication use;(3): Adjusted variables including any claim record with the above diagnoses or medication codes prior to the index date.

one observational study by Yi-Hsin Chan [34] published in 2018. The follow-up duration ranged widely from 30 days to 2.8 years. For RCTs, 49,560 patients received NOACs, and 35,001 patients received VKAs or acetylsalicylic acid. The characteristics of 3 included database studies were outlined in Table 2, enrolling 69,628 patients receiving NOACs and 35,294 patients taking warfarin. Inverse probability of treatment weights of propensity scores (IPTW) was applied to minimize the influence of confounding factors and heterogeneity of patient characteristics between comparison groups in the involved 3 database studies. As shown in Table 3, patient demographics were similar across 14 studies. The creatinine clearance of patients in the included studies was also presented, and most studies involved patients in different renal function. The quality assessment of included studies was of modest to high (Table S3-S4).

3.2. Incidence and risk of any and various forms of renal impairment

Totally, 922 patients (1.09%) were recognized as renal impairment in 11 included RCTs, of which 544 (1.10%) were NOACs users and 378 (1.08%) were VKAs or acetylsalicylic acid users. The pooled results of 14 studies showed that the use of NOACs was significantly associated with a lower risk of renal impairment compared with VKA/acetylsalicylic acid (HR: 0.67, 95%CI: 0.62–0.73 for random-effects model, I^2 = 75.6%) (Fig. 1). Results of narrow definition of renal impairment were accordant with the overall outcome (HR: 0.65, 95%CI: 0.60–0.71 for random-effects model, I^2 = 76.8%) (Fig. S2). Various forms of renal dysfunction were presented in Table 4. There were 12 forms of renal dysfunction in included studies, and acute renal failure, renal impairment and renal failure were the most reported forms. The incidence rate of individual forms of renal disorder was from 0.005% to 0.58%, and no significant difference was found between NOACs and comparator.

3.3. Subgroups, sensitivity, and meta-regression analyses

The overall result of subgroup analysis was summarized on Table 5, and the detailed results by study type, individual NOACs and different controls were presented in Figs. S3–S5. Considering the results in different study types, NOACs showed a significantly lower risk of renal impairment compared with VKAs/acetylsalicylic acid in both RCTs (HR: 0.83, 95%CI: 0.69–0.97) and observational studies (HR: 0.64, 95%CI: 0.58–0.69). Regarding individual NOACs, dabigatran (HR: 0.64, 95%CI: 0.56–0.72), rivaroxaban (HR: 0.66, 95%CI: 0.55–0.77) and apixaban (HR: 0.73, 95%CI: 0.59–0.87) were all associated with a significant lower risk of renal impairment except for edoxaban (HR: 0.79, 95%CI: 0.30–1.27). In terms of different control drugs, patients with VKAs, but not acetylsalicylic acid, showed a significantly increased renal impairment risk compared with NOACs. The results of sensitivity analyses were in line with the primacy outcome (Table 6, Figs. S6–S11). Sensitivity analyses showed that similar results were obtained regardless of which study or which kind of study was excluded from the primary analysis. Furthermore, no potential confounding of clinical characteristics was detected to impact the renal impairment outcome, indicating that mean age, percentage of male, heart failure, hypertension, diabetes, transient ischemic attack/systemic embolism, prior myocardial infarction, prior coronary heart disease, $CHADS_2$/CHA_2DS_2-VASc score, and initial renal function did not seem to contribute to heterogeneity (Table S5).

3.4. Publication bias

No evidence of publication bias was indicated based on Begg's test (z = 1.49, p = 0.137).

4. Discussion

Stroke prevention is the principal priority in the treatment of AF,

Table 3
Patient demographics and clinical characteristics of randomized trials and database studies.

Study (year)	Total number	Mean age (year)	Male (%)	HF (%)	Hypertension (%)	Diabetes (%)	Stroke/ TIA/SE (%)	Prior MI (%)	$CHADS_2$/ CHA_2DS_2-VASc	Ccr50-80 mL/min (%)	Ccr < 50 mL/min (%)
RE-LY 2009	18,040	71.5	63.6	32.0	78.9	23.3	20.0	16.6	2.10	59.6	18.8
ROCKET AF 2011	14,236	71.2	57.5	62.4	90.5	39.9	54.8	17.3	3.47	47.3	20.8
ARISTOTLE 2011	18,140	69.1	64.7	35.4	NR	25.0	19.4	14.2	2.10	35.4	13.9
AVERROES 2011	5578	69.9	58.5	38.8	86.4	19.6	13.6	NR	2.00	55.1	15.8
J-ROCKET AF 2011	1278	71.1	80.6	40.8	79.5	38	63.6	7.7	NR	51.3	22.2
ENGAGE AF-TIMI 48 2013	21,016	70.6	61.9	57.4	93.6	36.1	28.3	NR	NR	43.7	18.6
X-VERT 2014	1504	64.9	72.7	18.1	NR	20.3	2.7	8	NR	32.6	6.6
PIONEER AF-PCI 2016	2124	70.1	74.4	NR	NR	NR	NR	NR	NR	NR	6.6
RE-CIRCUIT 2018	635	59.2	74.8	10.2	54	10.0	NR	3.9	NR	NR	NR
EMANATE 2018	1456	64.6	66.8	NR	65.1	19.6	NR	NR	2.40	NR	NR
Yamashita 2012	265	69.4	82.6	NR	NR	NR	NR	NR	NR	NR	12.6
Yi-Hsin Chan 2016	19,932	75.4	57.7	15.5	87	41.5	32.9	3.2	4.14	NR	NR
Xiaoxi Yao 2017	9769	73	55.1	33.0	92.2	43.4	15.9	NR	4.04	NR	NR
Yi-Hsin Chan 2018	75,221	71.2	57.6	14.4	73.7	32.4	14.4	NR	3.21	NR	NR

HF: heart failure; TIA: transient ischemic attack; SE: systemic embolism; MI: myocardial infarction; Ccr: creatinine clearance; NR: not reported; 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; AVERROES: A Phase III Study of Apixaban in Patients With Atrial Fibrillation; ENGAGE AF-TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; X-VERT: eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion; PIONEER AF-PCI 2016: A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-CIRCUIT: Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy; EMANATE: Eliquis evaluated in acute cardioversion coMpared to usuAl treatmeNts for AnticoagulaTion in subjEcts with atrial fibrillation.

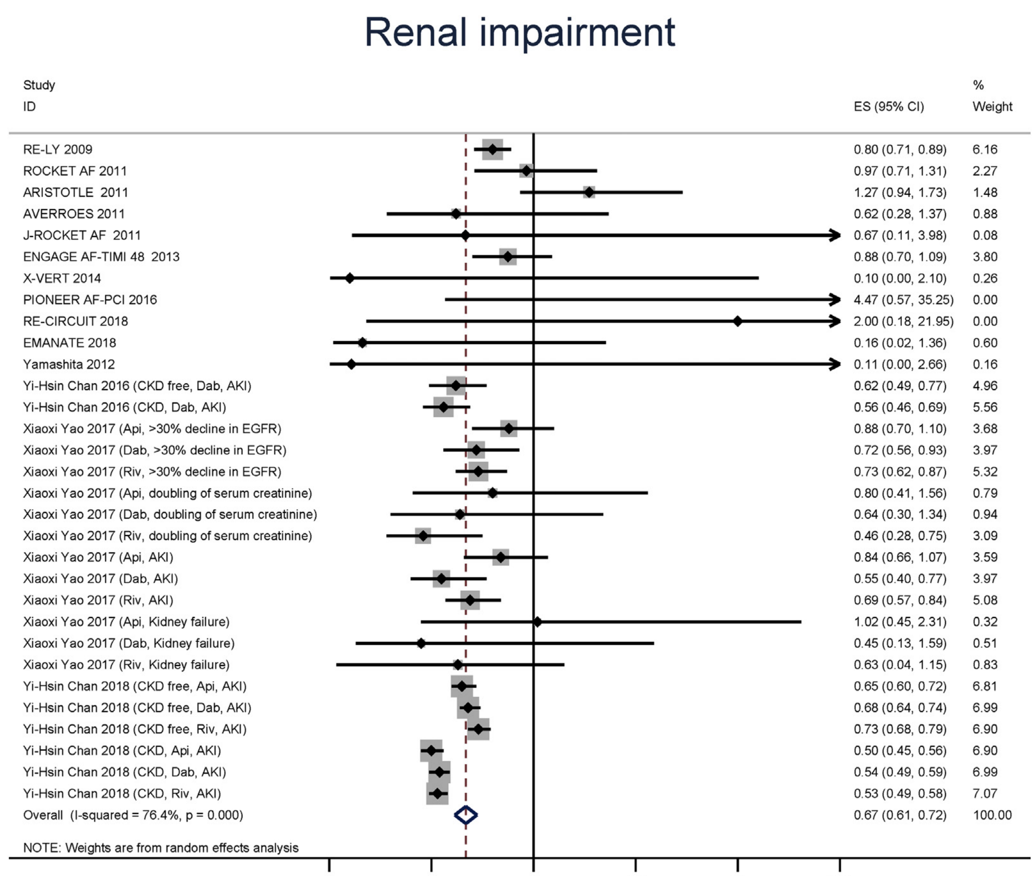

Fig. 1. Risk of renal impairment in patients with NOACs versus vitamin K Antagonists (VKAs)/acetylsalicylic acid. HR indicates Hazard ratio; 95%CI indicates 95% confidence interval.

Table 4
Hazard ratios by various forms of renal impairment.

Various forms of renal impairment	No. of studies	With NOACs therapy (%)[a]	With comparison therapy (%)[a]	HR (95%CI)	Homogeneity	
					I^2 (%)	p value
Renal failure	7	133/47103 (0.28%)	103/33314 (0.31%)	0.73 (0.49–0.96)	9.0	0.36
Acute renal failure	10	304/52213 (0.58%)	198/34872 (0.57%)	0.83 (0.56–1.10)	36.7	0.12
Chronic renal failure	5	40/45062 (0.09%)	34/31978 (0.11%)	0.64 (0.26–1.03)	0.0	0.69
Renal impairment	8	38/50490 (0.08%)	20/33652 (0.06%)	0.85 (0.17–1.53)	0.0	0.99
Nephritis	2	0/19153 (0.00%)	2/13123 (0.02%)	0.20 (0.03–2.02)	0.0	0.94
Nephropathy	3	5/33167 (0.02%)	1/20135 (0.005%)	1.55 (0.05–8.09)	0.0	1.00
Nephrotic syndrome	5	5/42651 (0.01%)	3/29316 (0.01%)	0.18 (0.03–1.41)	0.0	1.00
Acute prerenal failure	5	9/35208 (0.03%)	8/21471 (0.04%)	0.51 (0.05–1.28)	0.0	1.00
Postrenal failure	2	1/9823 (0.01%)	2/9773 (0.02%)	0.46 (0.04–4.03)	0.0	0.88
Renal disorder	1	1/12042 (0.01%)	0/5998 (0.00%)	1.49 (0.06–36.68)	–	–
Renal injury	3	3/35144 (0.01%)	3/22062 (0.01%)	0.28 (0.04–1.57)	0.0	0.98
Renal tubular necrosis	3	5/35144 (0.01%)	4/22062 (0.02%)	0.18 (0.05–1.17)	0.0	0.87

NOACs: Non-vitamin K Antagonist Oral Anticoagulants; HR: hazard ratio; 95%CI: 95% confidence interval.
[a] Data from RCTs.

particularly oral anticoagulation. Maintenance of adequate renal function is extremely important for AF patients receiving oral anticoagulant, as worsened renal function might increase the risk of both stroke and bleeding [35,36]. Therefore, the influence of oral anticoagulants on renal function is crucial to be understood for the safety of anticoagulation therapy. NOACs, possessing favorable property of thromboembolism prophylaxis and reduced bleeding risk, are being recommended as an optimal alternative to warfarin in AF [37]. Regretfully, little is known about the potential renal toxicity of NOACs in AF patients. In this study, we performed the first pooled analysis to merge current evidences from both RCTs and high-quality observational database studies for evaluating the association between the use of NOACs and the risk of renal impairment. The overall results suggested that the use of NOACs might lead to a decreased risk of renal impairment compared with VKAs or acetylsalicylic acid.

To date, evidences suggested that the use of oral anticoagulants, both warfarin and NOACs, might resulted in anticoagulant-related nephropathy (ARN), with the precise mechanism being not fully understood [38]. Although over-anticoagulation is considered to be associated with ARN, the pathological mechanisms might differ between warfarin and NOACs [39]. Warfarin inhibits the vitamin K-dependent proteins, including matrix G1a protein and growth arrest specific gene 6 (GAS-6). The inhibition of these proteins facilitates renovascular calcification, interferes with renovascular smooth muscle cell migration, and alters glomerular hemodynamics vulnerable to injury, which consequently result in the decline in renal function [34]. Differently, NOACs, such as dabigatran, could cause dose-dependent increase in serum creatinine in 5/6 NE rats, which was associated with vascular inflammation [38]. Evidence from animal studies revealed that dabigatran might induce AKI through two major pathogenic mechanisms. One is the tubular obstruction by RBCs, and the other is the involvement of protease-activated receptor 1(PAR-1), which is the thrombin receptor on endothelial cells [40]. Dabigatran decreases thrombin activity, thus inhibiting PAR-1. And the selective inhibition of PAR-1 results in increase creatine, hematuria, and tubular RBC casts

Table 6
Sensitive analyses.

	HR (95%CI)
Omitted trial	
RE-LY 2009	0.69 (0.6–0.79)
ROCKET AF 2011	0.70 (0.61–0.79)
ARISTOTLE 2011	0.69 (0.61–0.77)
AVERROES 2011	0.72 (0.63–0.81)
J-ROCKET AF 2011	0.72 (0.62–0.81)
ENGAGE AF-TIMI 48 2013	0.70 (0.60–0.79)
X-VERT 2014	0.72 (0.63–0.81)
PIONEER AF-PCI 2016	0.72 (0.62–0.81)
RE-CIRCUIT 2018	0.72 (0.63–0.81)
EMANATE 2018	0.72 (0.63–0.82)
Yamashita 2012	0.72 (0.63–0.81)
Yi-Hsin Chan 2016	0.75 (0.64–0.85)
Xiaoxi Yao 2017	0.72 (0.61–0.84)
Yi-Hsin Chan 2018	0.75 (0.64–0.85)
Excluded trial	
Acetylsalicylic acid as control studies	0.72 (0.63–0.81)
Catheter ablation studies	0.72 (0.63–0.81)
Cardioversion	0.73 (0.64–0.82)
PCI studies	0.72 (0.62–0.81)
Low dosage arms of NOACs	0.67 (0.61–0.72)

Table 5
Subgroup analyses.

Subgroup	No. of studies	With NOACs therapy (%)	With comparison therapy (%)	HR (95%CI)	Homogeneity	
					I^2 (%)	p value
Study type						
RCTs	11	544/52609 (1.03%)	378/35001 (1.08%)	0.82 (0.71–0.93)	26.9	0.18
Database studies	3	–	–	0.64 (0.58–0.69)	77.6	0.00
NOACs						
Dabigatran	5	135/15429 (0.87%)	71/6336 (1.12%)	0.64 (0.56–0.72)	73.0	0.00
Rivaroxaban	6	91/10140 (0.9%)	89/8960 (0.99%)	0.66 (0.55–0.77)	78.9	0.00
Apixaban	5	102/11895 (0.86%)	88/11843 (0.74%)	0.73 (0.59–0.87)	81.0	0.00
Edoxaban	2	215/14410 (1.49%)	124/7141 (1.74%)	0.79 (0.30–1.27)	19.9	0.26
Controls						
VKAs	10	534/49802 (1.07%)	362/32210 (1.12%)	0.67 (0.62–0.72)	77.2	0.00
Acetylsalicylic Acid	1	10/2807 (0.36%)	16/2791 (0.57%)	0.62 (0.08–1.16)	–	–

[39]. Beyond that, a recent meta-analysis indicated that the use of NOACs showed similar risk of renal failure to traditional anticoagulants such as warfarin and low-molecular-weight heparin [14]. Meanwhile, studies suggested that patients taking NOACs would be at high risk of renal failure with excessive therapeutic range of anticoagulation [38,39]. Accordingly, regular monitoring of renal function is crucial to avoid prescribing NOACs at inappropriately high dose.

All the NOACs have some degrees of renal excretion [10], nevertheless, whether NOACs is associated with a lower risk of renal impairment remains largely speculative. Several studies have reported data related to this issue. Warfarin was associated with a greater decline in eGFR than either low-dose (HR: 0.81, 95% CI: 0.69–0.96) or standard-dose dabigatran (HR: 0.79, 95% CI: 0.68–0.93) in the post hoc analysis of RE-LY trial [13], while apixaban showed a similar risk of acute renal failure compared with warfarin in ARISTOTLE trial (RR: 0.97, 95% CI: 0.88–1.07) [14]. Moreover, one observational study of total 75,221 AF patients has compared NOACs with warfarin for AKI, and found a lower risk with NOACs [34]. To obtain a robust conclusion, a large size of patients is need as the relatively low incidence of ARN. In recent years, several real-world studies concerning about the risk of renal dysfunction in AF patients receiving anticoagulants have been published, and sufficient information based on large patient sample size was available to dig this issue [32–34]. In this study, we collected about 190,000 patients from 11 RCTs and 3 high-quality observational studies to estimate the risk of renal impairment in AF patients with NOACs. The pooled results clearly revealed that NOACs were associated with lower risk of adverse renal outcomes than VKAs/acetylsalicylic acid. However, it is worth noting that I^2 values of 76.4% represented considerable heterogeneity, which might result from the varying degrees of nephroprotective effect of NOACs in different studies. Most importantly, all the HRs of included studies were lower than 1 except for those in ARISTOTLE trail, suggesting that the estimates of decreased risk were consistent across studies.

Concerning individual NOACs, dabigatran, rivaroxaban and apixaban were all associated with a lower risk of renal impairment except for edoxaban. The negative result of edoxaban mainly came from the limited sample size and correspondingly underpowered statistical efficiency. These results suggested a potential class effects on renal function protection across NOACs, independent of the degree of renal excretion.

The benefit of oral anticoagulants in reducing stroke and mortality is now well established in AF patients. Renal function needs to be diligently monitored for AF patient taking whether warfarin or NOACs, to detect changes in renal function and adapt the dose accordingly [37]. NOACs, including dabigatran, rivaroxaban, apixaban and edoxaban, showed consistent efficacy and safety in patients with mild to moderate CKD versus non-CKD patients [37]. And rivaroxaban, apixaban and edoxaban have been approved in Europe in patients with severe CKD (CrCl 15–29 mL/min) with reduced dose regimen [37]. Whereas, evidence was lack for the NOACs use in AF patients with end-stage CKD or hemodialysis, which in turn, limited the use of NOACs in these patients. Taken together, the use of NOACs and the progress of renal function could interplay with each other. Of note, studies regarding the use of NOACs in patients with renal impairment seemed to be the focus, while the influence of NOACs use on the renal function was neglected. In fact, change in renal function during the use of NOACs should be concerned about, which is crucial to the safety of AF patients, as decreased renal function might result in the interrupt of anticoagulation or even fatal bleeding. And further RCTs or database studies were needed to strengthen the evidence on this aspect.

Several limitations should be addressed in this study. Firstly, the heterogeneity between RCTs and observational studies were inevitable and need to be considered. Various confounding factors were adjusted in observational studies with different methods, posing a challenging for comparability among studies. Nonetheless, a meta-regression analysis was performed to estimate potential effect modifiers in clinical characteristics, and no significant confounding on outcomes was identified. Secondly, none of RCTs included in this study was specially designed to evaluate the influence of NOACs on renal function. As a result, a clear and uniform definition of renal impairment, as well as incomprehensive collection of renal data across trials were unattainable, which might introduce certain bias. Moreover, the mean duration of follow-up was relatively insufficient, with three trials follow-up < 2 months, which might result in underestimation of effects of NOACs on renal function. Thirdly, 16 RCTs and 61 database studies were excluded in the selection process due to the unavailability of renal function data, which might lead to reduced power of statistics.

5. Conclusions

The use of NOACs might confer a lower risk of renal impairment compared with VKA or acetylsalicylic acid in patients with AF. Further specialized designs of RCTs as well as real-world experiences are necessary to draw a robust association between the use of NOACs and the decreased risk of renal impairment.

Author contributions

Jun Pu, Hou-Wen Lin, Zhi-Chun Gu and Ying-Li Zheng are the guarantors of the entire manuscript. Chi Zhang and Zhi-Chun Gu conceived and designed the study, collected and analyzed the data, and wrote the manuscript. Zheng Ding, Long Shen, and Mang-Mang Pan collected the data and performed the statistical analysis. All the authors read and approved the final manuscript.

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Disclosures

The authors report no conflicts of interest in this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.12.010.

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