The impact of renal function on efficacy and safety of new oral anticoagulant in atrial fibrillation patients

A systemic review and meta-analysis

Yi-yue Gui, MD, Song Zou, BD, Wen-long Yang, BD, Shen-zhen Gong, MD, Zhi-fu Cen, MD, Zhong-hui Xie, BD, Kai-jun Cui, MD*

Abstract

Background and objectives: This meta-analysis was to investigate the efficacy and safety of new oral anticoagulant (NOAC) in atrial fibrillation (AF) patients with renal function insufficiency, and to explore whether renal decline occurs in AF patients with NOAC and its impact on outcomes.

Methods and results: In AF patients with mild renal insufficiency, the NOAC was associated with significantly lower rates of stroke (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.67–0.91; P < .05). Lower rates of bleeding were significantly observed in NOAC group (OR, 0.85; 95% CI, 0.75–0.97; P < .05). In AF patients with moderate renal impairment, similar results were revealed (OR for stroke or systemic embolism, 0.80; 95% CI, 0.67–0.95, P < .05; OR for major bleeding, 0.78; 95% CI, 0.59–1.03; P = .07). During the follow-up, pooled data revealed that NOAC showed a less renal toxicity, but the difference did not reach statistical significance (creatinine clearance decline: −0.12 mL/min [−0.84, 0.61 mL/min]). We have revealed that the NOACs were associated with significantly lower rates of stroke or systemic embolism (hazard ratio [HR], 0.66; 95% CI, 0.42–0.98; P < .05) and lower rates of bleeding (HR, 0.93; 95% CI, 0.70–1.16; P = .153) in AF patients with worsening renal function.

Conclusions: NOAC may have the potentiality to be at least as effective as warfarin and may equal safety outcomes in AF patients with renal impairment. Renal decline during therapeutics may be less likely happened in NOAC than warfarin dose. NOAC may reveal good efficacy and safety outcomes in these scenarios. Further detailed research is needed to gain more clear profile on this new anticoagulant.

Abbreviations: AF = atrial fibrillation, ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, CrCl = estimated glomerular filtration rate, ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48, HR = hazard ratios, NOAC = new oral anticoagulant, OR = odds ratios, RCT = randomized controlled studies, RE-LY = Randomized Evaluation of Long-Term Anti-coagulation 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, SRF = stable renal function, WRF = worsening renal function.

Keywords: new oral anticoagulant, renal insufficiency, worsening renal function

1. Introduction

Nowadays, chronic kidney disease, with a prevalence of nearly 10% in adult’s population,[1] carries a high risk of cardiovascular diseases, including atrial fibrillation (AF). Impaired renal function is associated with an increased risk of thromboembolic events in nonvalvular AF.[2] Oral anticoagulation therapy is recommended in current medical practice in AF patients at potential risk of stroke[3]; however, impaired renal function renders a substantially increased risk of major bleeding[4] and often results in underutilization of oral anticoagulants in AF patients.[5]

Vitamin K antagonists, unfractionated heparin, or low-molecular-weight heparin are the most commonly prescribed anticoagulants in these scenarios, but limitations sustain in each therapeutic.[6–9] In patients with moderate and severe renal insufficiency, use of warfarin is associated with an increased risk of bleeding complications, and a clear benefit versus risk of using warfarin in patients with renal insufficiency and AF has not been investigated.[10,11] Several new oral anticoagulants (NOACs) have been approved for clinical practice and others are in development.[12–15] The advantages of these agents are convenient oral dosing, predictable pharmacokinetics, avoidance of
routine coagulation monitoring, noninferior or superior efficacy, and acceptable safety, including a lower risk of intracranial hemorrhage.

Although anticoagulation with warfarin or the NOAC, which have been rapidly adopted into routine clinical practice,\cite{16} patients exhibit a decline in renal function over time that appears to be greater in those taking warfarin.\cite{17} Whether NOAC or warfarin carries more renal toxicity during therapeutics is not known. Moreover, it is unknown whether outcomes differ among patients with worsening renal function (WRF) compared with those with stable renal function (SRF) while taking a NOAC or warfarin.

There are knowledge gaps in AF patients with renal impairment, and NOACs variable dependence on renal clearance leaves efficacy and safety less certain compared with conventional anticoagulants.\cite{18,19} Several randomized controlled studies (RCTs) demonstrated that NOAC might be more advantageous than warfarin.\cite{18} However, these trials have been conducted to evaluate modified dosing regimens in renal insufficiency patients.\cite{13,14} Therefore, we conducted a meta-analysis of RCTs focusing on the efficacy and safety of NOACs in patients with renal impairment, and explored the renal change during oral anticoagulation in AF patients and its effect on outcomes.

2. Methods

2.1. Literature strategy

A comprehensive search of the PubMed, Cochrane Systematic Reviews, Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, and Web of Science published between January 1, 2001 and March 24, 2019 was performed independently by 2 team crews (SZ, WLY). The search strategy, study selection, and analysis criteria adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.\cite{22} We selected the following search terms and/or keywords: new oral anticoagulant, oral thrombin inhibitor, oral factor Xa inhibitor, dabigatran, rivaroxaban, edoxaban, and apixaban. In addition, reference of review articles, meeting abstracts, letter, editorials was also searched. The hospital ethics review committee approved this study.

2.2. Selection criteria

Inclusion in this analysis required the following: phase III RCTs evaluating dabigatran, rivaroxaban, edoxaban, or apixaban; \( \geq 1 \) comparator (warfarin, unfractionated heparin, low-molecular-weight heparin, aspirin, or placebo); efficacy or safety endpoint data in AF patients with renal impairment; and renal change was reported during oral anticoagulation.

2.3. Data extraction

All data included in studies were independently extracted and assessed for further analysis by 2 reviewers (SZG, ZFC) using a standardized protocol, and disagreements were resolved by discussion with a third reviewer (ZHX). From each study, information about the baseline patient characteristics (age, sex, baseline renal function, prior warfarin used, previous aspirin used, CHADS2, heart failure, diabetes mellitus, baseline stroke, previous myocardial infarction), study design, follow-up duration was extracted and tabulated. We assessed risk of bias as recommended in the Cochrane Handbook of Systematic Reviews.\cite{22} Concealment of randomization, blinding, loss to follow-up, selective outcome reporting, use of unvalidated outcome measures, and stopping early for benefit were considered in the risk of bias assessment.

The Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) was a randomized trial designed to compare 2 fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin in patients who had AF and were at increased risk for stroke.\cite{12} In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,\cite{13} apixaban was compared with warfarin for the prevention of stroke or systemic embolism in patients with AF and at least 1 additional risk factor for stroke. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicenter, randomized, double-blind, double-dummy, event-driven trial.\cite{14} J-ROCKET AF was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter clinical trial that evaluated the safety of rivaroxaban versus dose-adjusted warfarin.\cite{23} The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial was a 3-group, randomized, double-blind, double-dummy trial comparing 2 dose regimens of edoxaban with warfarin.\cite{15}

Trials of rivaroxaban, dabigatran, and edoxaban excluded patients with creatinine clearance (CrCl) \(< 30\, \text{mL/min}\), and the trial of apixaban excluded those with CrCl \(< 25\, \text{mL/min}\) and did not report outcomes separately for participants with CrCl 25 to 29 mL/min; therefore, we set up 50mL/min as cutoff value for quantitative analysis. Renal function beyond 50 mL/min was categorized as mild renal impairment, and below the one as moderate renal impairment. With regard to renal function change, only 3 studies reported outcome data.\cite{17,24,25} In terms of WRF, we defined WRF as a decrease of \( > 20\% \) in CrCl from the baseline measurement at 12 months’ follow-up.

2.4. Data synthesis and analysis

The principal efficacy outcomes were stroke or systemic embolism. The primary safety outcome was major bleeding. Stroke was defined as a nontraumatic focal neurologic deficit lasting \( \geq 24\) hours. Diagnosis of major bleeding was based on the International Society on Thrombosis and Hemostasis criteria.\cite{16} Moderate renal insufficiency was defined as creatinine clearance (estimated glomerular filtration rate [eGFR]) of 30 to 49 mL/min, and mild renal insufficiency as eGFR \( \geq 50 \) to 79 mL/min (as classified in the original trials and based on European Medicines Agency classification)\cite{27} using the Cockcroft-Gault formula. GFR was estimated from serum creatine (SCr)\cite{28} and the following equations were used. Cockcroft-Gault equation: GFR (\( \text{mL/min} \)) = \( \frac{140 - \text{age} \text{[years]}}{\text{weight} \text{[kg]}} \times \frac{72}{\text{SCr} \text{[mg/dL]}} \)). With regard to renal change during clinical trials, we defined WRF as a decrease of \( > 20\% \) in CrCl from the baseline measurement at 12 months’ follow-up, SRF as \( \leq 20\% \) CrCl change. We analyzed the longest available follow-up data from individual trials according to intention-to-treat.

Data from each study were combined using a random-effects model to estimate pooled odds ratios (ORs) or hazard ratios (HRs) and respective 95% confidence intervals (CIs). Heterogeneity across trials was identified using I\(^2\) statistics, considering I\(^2\)
<25% as low and \( I^2 > 75\% \) as high heterogeneity and the Cochran Q (\( P \leq .1 \)) as significant for each outcome. Publication bias was evaluated using the Egger regression test and visual inspection of asymmetry in funnel plots. Statistical analyses were performed using RevMan 5.2.4 software with 2-tailed \( P \) values <.05 considered significant.

### 3. Results

#### 3.1. Characteristics of included trials

Our search yielded 1121 results. After electronic deduplicate, 814 studies were remained. A further detailed abstract and full-text assessment led to 5 randomized trials to be included (Fig. 1). Therefore 72,959 nonvalvular AF patients randomized to a NOAC or warfarin were selected for meta-analysis. All included studies were judged at “low risk” of bias. Baseline characteristics are listed in Table 1. A total of 43,050 participants received the NOAC and 29,909 participants the warfarin. The average age of patients was similar between trials as was the proportion of women recruited. However, the underlying risk for stroke differed significantly across the trials as shown by the proportion of patients with CHADS2 scores of \( \geq 3 \).

Median follow-up ranged from 1.8 years to 2.8 years and the median time in therapeutic range in patients in the warfarin groups ranged from 58% to 68%.

#### 3.2. Outcomes in renal function impairment group

There were 53,028 subjects with mild renal function impairment, among them 28,871 randomized to NOAC arm and 24,157 randomized to warfarin arm. There were 747 stroke or systemic embolism events (2.59%) happened in NOAC group, and 796 events (3.30%) in warfarin group. Meanwhile, there were 1387 major bleeding events (4.81%) identified in NOAC group, and 1332 events (5.52%) in warfarin group. In AF patients with mild renal insufficiency, the NOACs were associated with significantly lower rates of stroke or systemic embolism than conventional anticoagulants (Fig. 2A, OR, 0.78; 95% CI, 0.67–0.91; \( P < .05 \)). In terms of major bleeding, lower rates of bleeding were significantly observed in NOAC group compared with warfarin (Fig. 2B; OR, 0.85; 95% CI, 0.75–0.97; \( P < .05 \)).

There were 12,532 subjects with moderate renal function impairment, among them 6933 randomized to NOAC arm and 5599 randomized to warfarin arm. There were 282 stroke or systemic embolism events (4.06%) happened in NOAC group,
and 286 events (5.10%) in warfarin group. Meanwhile, there were 535 major bleeding events (7.72%) identified in NOAC group, and 508 events (9.07%) in warfarin group. In AF patients with moderate renal impairment, the NOACs were associated with significantly lower rates of stroke or systemic embolism than conventional anticoagulants (Fig. 2C, OR, 0.80; 95% CI, 0.67–0.95; \(P < .05\)). In terms of major bleeding, there was a trend of lower rates of bleeding in NOAC group compared with warfarin (Fig. 2D, OR, 0.78; 95% CI, 0.59–1.03; \(P = .07\)).

3.3. Renal function change during study and its relation to outcomes

Due to lack of data on renal function change of edoxaban study, we pooled data from dabigatran, rivaroxaban, and apixaban studies. In all population among RE-LY, ROCKET-AF, and ARISTOTLE trials, a trend of renal impairment could be seen after 12 months follow-up (mean for CrCl change during 12 months’ follow-up: –1.87 mL/min [11.56 mL/min], –3.9 mL/min [14.9 mL/min], –1.02 mL/min, respectively). In subjects randomized to NOAC, we could observe an impaired renal change in dabigatran, rivaroxaban, and apixaban (mean and standard difference: –1.82 mL/min [11.1 mL/min], –3.5 mL/min [15.1 mL/min], –1.42 mL/min [10.12 mL/min], respectively). In subjects randomized to warfarin, we could observe an impaired renal change in 3 trials (mean and standard difference: –1.94 mL/min [9.79 mL/min], –4.3 mL/min [14.6 mL/min], –0.92 mL/min [10.27 mL/min], respectively). Pooled data revealed that compared with warfarin, NOAC showed a less renal toxicity, but the difference did not reach statistically significance (Fig. 3A, CrCl change mean difference: –0.12 mL/min [–0.84, 0.61 mL/min]).

**Figure 2.** NOAC versus warfarin in (A) stroke of systemic embolism, or (B) major bleeding for AF patients with mild renal insufficiency; (C) stroke of systemic embolism, or (D) major bleeding for AF patients with moderate renal insufficiency; AF = atrial fibrillation; NOAC = new oral anticoagulant.
Figure 3. NOAC versus warfarin (A) in CrCl change during therapeutics; (B) WRF versus SRF in stroke or systemic embolism, or (C) major bleeding. CrCl = creatinine clearance, NOAC = new oral anticoagulant, SRF = stable renal function, WRF = worsening renal function.
3.4. Efficacy and safety Outcomes of WRF and SRF in NOAC and warfarin

During the follow-up, a total of 9720 (21.8%) patients had WRF (eGFR decline more than 20%), whereas a total of 34,793 (78.2%) patients had SRF (no WRF). In AF patients, the WRF was associated with higher rates of stroke or systemic embolism than SRF (Fig. 3B, HR, 1.27; 95% CI, 1.04–1.50; \( P = .316 \)). Moreover, in terms of major bleeding, higher rates of bleeding were significantly observed in WRF group compared with SRF (Fig. 3C, HR, 1.23; 95% CI, 1.10–1.35; \( P < .05 \)).

Subgroup analysis was performed to assess the efficacy and safety outcomes in AF patients with WRF or SRF. In subjects with SRF, we have observed that the NOACs were associated with significantly lower rates of stroke or systemic embolism than conventional anticoagulants (Fig. 4A, HR, 0.72; 95% CI, 0.61–0.83; \( P < .05 \)). In terms of major bleeding, lower rates of bleeding were significantly observed in NOAC group compared with warfarin (Fig. 4C, HR, 0.80; 95% CI, 0.72–0.89; \( P < .05 \)). However, in subjects with WRF, we have observed that the NOACs were associated with lower rates of stroke or systemic embolism than conventional anticoagulants (Fig. 4B, HR, 0.66; 95% CI, 0.42–0.89; \( P < .05 \)). In terms of major bleeding, lower rates of bleeding were observed in NOAC group compared with warfarin (Fig. 4D, HR, 0.93; 95% CI, 0.70–1.16; \( P = .153 \)), although the difference was not statistically significant.

4. Discussion

In this novel comprehensive analysis, we firstly evaluated the efficacy and safety of NOAC in AF patients with renal insufficiency comparable with warfarin, and firstly pooled data regarding renal function change during drug therapeutics and its effect on outcomes from several RCTs up to date. We demonstrated important findings in those subgroups of AF patients. First, NOAC, a new class of anticoagulant, exhibited lower rates of stroke or systemic embolism and lower rates of major bleeding compared with warfarin in AF patients with mild or moderate renal impairment. Therefore, NOAC might be at least effective as well as safe in this population. Second, certain percentages of AF patients with oral anticoagulant progressed proportions of renal function decline, irrespective of baseline renal function. Routine screening before and during anticoagulation is important, and dosing titration is necessary for renal impairment patients. Third, in AF patients with WRF, the risk of stroke or major bleeding is increasing. NOAC showed a good efficacy potentiality and preserved safety comparable with warfarin in WRF patients.

In AF patients, renal function is intensively associated with thromboembolic and bleeding events\(^8,32\); renal dysfunction is a risk factor for incident AF, which in turn is associated with progressive renal dysfunction.\(^7\) Therefore, it is important to understand whether renal function affects the safety and efficacy of the therapeutic options for the prevention of stroke and major bleeding events in AF patients. Warfarin is metabolized by the liver, primarily through CYP 2C9, and inactive metabolites are then excreted in the urine. Although warfarin elimination is therefore not governed by the kidneys, there is conflicting evidence from observational studies on the safety and efficacy of warfarin for AF in patients with chronic kidney disease.\(^33\) Currently, 4 NOACs are partially eliminated by renal clearance; dabigatran 80%, rivaroxaban 35%, apixaban 25%, and edoxaban 50%.\(^12–15\) In patients with impaired renal function,
previous studies revealed an increase in the area under the plasma concentration curve or maximal plasma concentration for NOACs. Based on these pharmacological data, most RCTs evaluating these NOACs modified dosing regimens in these AF patients with renal insufficiency.

We revealed that NOACs might have a more acceptable efficacy and safety profile than warfarin, when evaluated in AF patients with renal insufficiency, which is consistent in analysis derived from RCTs.[11,28–31,34] In patients with moderate renal impairment, these new anticoagulants prevent them from thromboembolic events, and are equally safe as warfarin. Given that the most RCTs excluding patients with severe renal insufficiency, no evidence is available for patients with stage IV renal impairment regarding efficacy and safety endpoints, and current clinical practice avoids NOAC in these scenarios. Similarly, there is knowledge gap in dialysis patients upon whether NOAC shows better safety or not.

In AF patients with anticoagulant, WRF is seen in a certain percentage of population. Our analysis had revealed that the risk of thromboembolic and bleeding is increasing with WRF, which is consistent with other subanalysis from RCTs.[17,24–25] So far, the accumulated data point to an incidence of a clinically significant worsening renal failure of approximately 15% to 25%.[35] Data from dabigatran study[17] showed that WRF happened in approximately 13.18% of subjects with NOAC and 13.69% with warfarin, so both NOAC and warfarin exhibit some kind of renal toxicity. In the post hoc analysis of RE-LY trial[17] 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), whereas apixaban showed a similar risk of acute renal failure compared with warfarin in the ARISTOTLE trial (RR: 0.97, 95% CI: 0.88–1.07).[25] In AF patients with WRF, our pooled data revealed that NOAC prevented thromboembolic events and preserved safety compared to warfarin.

There are some differences been observed across studies, partially due to participants’ age, burden of comorbidities, and others, as well as different follow-up time, the applied definition of a worsening of renal function, the frequency of renal function measurements, and how renal function is estimated (Cockcroft-Gault, CKD-EPI, or Modification of Diet in Renal Disease equations, and so on). In the RE-LY study[17] older age and certain burden of cardiovascular comorbidities are associated with WRF.

Some limitations existed in this quantitative analysis. There are some differences across RCTs regarding protocols, criteria for mild or moderate renal insufficiency, definition of efficacy and safety outcomes, and baseline characteristics of randomized patients. Several of our conclusions are limited by wide CIs and some degree of statistically heterogeneity, which needs further validation. Regarding renal insufficiency, more detailed renal disease needs to be incorporated. Most of the evidence derived from westerners, so careful assessment should be noticed when these evidences applied in Asians. Finally, all the studies are derived from post-hoc analysis from RCTs; therefore, our findings must be considered as hypothesis-generating.

5. Conclusions

This pooled analysis gives us insight into the use of NOAC in AF patients with renal insufficiency. NOACs, titrated in recommended doses, may have the potentiality to be at least as effective as warfarin in preventing stroke and equal bleeding risk compared with warfarin. Renal decline during therapeutics may be less likely happened in NOAC than warfarin dose, and NOAC may reveal good efficacy and safety outcomes in these scenarios. Further detailed research is needed to gain more clear profile on this new anticoagulant in AF patients.

Author contributions

Conceptualization: Yi-yue Gui, Kai-jun Cui.
Data curation: Song Zou.
Formal analysis: Wen-long Yang.
Investigation: Shen-zhen Gong.
Software: Zhi-fu Cen.
Validation: Zhong-hui Xie.

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