Net clinical benefit analysis of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and chronic kidney disease

Protocol for a systematic review and meta-analysis

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Abstract
Background: Atrial fibrillation (AF) is increasingly prevalent in chronic kidney disease (CKD) patients. The efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in AF and CKD patients remains unknown. This systematic review and meta-analysis will mainly assess net clinical benefit (NCB) property of NOACs versus warfarin in patients with AF and CKD by a pooled-analysis.

Methods: We will search Medline, Embase, Cochrane Library, and Clinical Trials.gov Website comprehensively for eligible randomized controlled trials that report the efficacy and safety outcomes according to renal function of NOACs. Relative risks and their 95% confidence intervals will be calculated using fixed- and random-effects models. Subgroup, sensitivity, and regression analyses will be performed to evaluate intertrial heterogeneity and bias of the results. NCB that balance stroke/systemic embolism (SSE) and major bleeding will be calculated using Singer’s method.

Results: This systemic review and meta-analysis will evaluate the NCB of NOACs versus warfarin via SSE, major bleeding and all-cause death in patients with CKD.

Conclusions: This study will provide new evidence for clinical profile of NOACs on SSE, major bleeding, all-cause death, and NCB in CKD patients.

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Abbreviations: AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, NCB = net clinical benefit, NOAC = non-vitamin K antagonist oral anticoagulant, OAC = oral anticoagulation, RCT = randomized controlled trial, SSE = stroke/systemic embolism.

Keywords: atrial fibrillation, chronic kidney disease, net clinical benefit, non-vitamin K antagonist oral anticoagulants

1. Introduction
The prevalence of atrial fibrillation (AF) is increasingly higher in chronic kidney disease (CKD) patients. Of note, both AF and CKD increase the risk of stroke and systemic thromboembolism. CKD is associated with an enhanced risk of cardiovascular disease, and it is an independent risk factor of thromboembolism and bleeding. In addition, CKD is widely considered as a predictor for the low time in therapeutic range (TTR) and superimposed platelet dysfunction in AF patients treated with warfarin. Thus, patients with concomitant AF and CKD are at a higher risk of stroke or embolism as well as bleeding.

Stroke/systemic embolism (SSE) is a leading cause of mortality and morbidity, non-vitamin K antagonist oral anticoagulants (NOACs), due to their favorable profile of efficacy and safety, represents an optimal therapeutic option in AF. In recent years, NOACs account for most of oral anticoagulants prescribed for patients with newly diagnosed AF. Meanwhile, the use of NOACs in CKD is also increasing in spite of the limited evidence on these fragile patients. It is acknowledged that renal clearance of NOACs are dabigatran 80%, edoxaban 50%, rivaroxaban 36%, apixaban 27%, respectively. Therefore, the accumulation of free blood concentration may lead to a subsequent
bleeding risk in CKD patients.\textsuperscript{[9]} Previous studies only evaluated the efficacy and safety of individual NOACs on thrombotic and bleeding risk in general AF patients.\textsuperscript{[10,11]} There are no head-to-head risk comparisons among the NOACs in CKD patients. Currently, the direct data on NOACs from randomized clinical trials (RCTs) and real world studies in patients with concomitant AF and CKD are limited. Only a few studies assessed the efficacy and safety of individual NOACs across CKD subgroup analysis.\textsuperscript{[12,13]} Compared with warfarin, NOACs have been proved to reduce SSE and major bleeding in CKD patients, but number of patients needed to treat (NNT) and net clinical benefit (NCB) has not been explored.\textsuperscript{[14,15]} In recent years, the NCB property of NOACs has not been explored.\textsuperscript{[16]} Noteworthy, Pelliccia et al reported that apixaban and dabigatran were superior to warfarin in terms of the NCB.\textsuperscript{[17]}

In recent years, the comprehensive risk of SSE and bleeding in AF.\textsuperscript{[16]} Noteworthy, Pelliccia et al reported that apixaban and dabigatran were superior to warfarin in terms of the NCB.\textsuperscript{[17]}

Current evidence on NCB of AF is derived mainly from observational studies and registry-based cohorts, data from RCTs, especially for patients with AF and CKD is quite limited.\textsuperscript{[18–20]} Hence, this systematic review and meta-analysis will mainly assess the NCB property of NOACs in patients with concomitant AF and CKD by a pooled analysis and available findings might provide a viable option of NOACs in patients with AF and CKD.

### 2. Methods

#### 2.1. Data sources and search strategy

The study will be conducted in accordance with the standards of the preferred reporting items for systematic reviews and meta-analyses statement. Medline, Embase, and Cochrane Library will be comprehensively searched to identify all potentially eligible studies. The search strategy will be conducted as follows: we will include the following terms: “NOACs,” “Pradaxa” or “dabigatran” or “Xarelto” or “rivaroxaban” or “Eliquis” or “apixaban” or “Savaysa” or “edoxaban” or “Bveyxxa” or “betrixaban” or “Non-vitamin K antagonist oral anticoagulants” or “direct oral anticoagulants” or “NOACs” or “DOACs” or “novel oral anticoagulants” or “new oral anticoagulants” or “factor Xa inhibitors” or “factor IIa inhibitors.” For the theme “atrial fibrillation,” we will use “atrial fibrillation” or “AF.” For the theme “RCTs,” we will include the following terms: “randomized controlled trial” or “controlled clinical trial” or “clinical trial.” Then we will use the Boolean operator “AND” to combine the 3 comprehensive search themes. In addition, unpublished trials will be identified from the ClinicalTrials.gov Website.

#### 2.2. Study selection

Studies will be selected if they met the following inclusion and exclusion criteria:

1. study involving phase III RCTs of patients with AF and receiving one of the NOACs as compared to warfarin;
2. RCTs that include patients with mitral stenosis or prosthetic cardiac valves, mean or median follow-up <6 months, <200 subjects, and NOAC phase II will be excluded. For trials reporting multiple publications, the most relevant data will be extracted.

### 2.3. Study outcomes

Pre-specified outcomes are SSE, major bleeding, all-cause death, and NCB. Major bleeding is defined according to the International Society of Thrombosis and Hemostasis. The data analysis will follow the intention-to-treat principle, creatinine clearance (CrCl) represents renal function following the Cockcroft-Gault formula, and classified as no CKD group (CrCl>80 ml/min), mild CKD group (CrCl=50–80 ml/min), and moderate CKD group (CrCl 30–50 ml/min).

### 2.4. Data extraction and quality evaluation, and bias assessment

Data will be extracted, including year of publication, duration of follow up, number of patients, mean age, sex, AF type, mean CHADS\textsubscript{2} score, risk factors, and prior medicine use. The methodological quality of trials will be assessed according to the Cochrane Collaboration Risk of Bias Tool, which focus on random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.\textsuperscript{[21]} Funnel plots will be generated to assess for publication bias.\textsuperscript{[21]}

### 2.5. Data analysis

Relative risks and 95% confidence intervals of the outcomes in NOACs versus warfarin will be calculated using fixed- and random-effects models. Statistical heterogeneity will be assessed with $I^2$ test. $P$ of $>50\%$ indicate considerable heterogeneity, and $P$ value of $<0.05$ represents a significant heterogeneity.\textsuperscript{[22]} Subgroup analyses will be conducted following renal function group. The number of patients NNT to prevent 1 event will be calculated as: $(1/\text{absolute risk reduction} ) \times 100$, where absolute risk reduction will be rate difference (event rates per 100 patients-year on warfarin minus event rates per 100 patients-year on NOACS).\textsuperscript{[18]} The NCB of NOACs compared with warfarin will be calculated using the follow 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 is event rates per 100 patients-year. We will assign their weighting factor of 1.5, and also provide additional sensitivity analysis using weighted factor of 1.0 and 2.0.\textsuperscript{[18]} Meta-regression analysis will be performed to explore the influence of these factors on outcomes. Sensitivity analysis will be conducted to evaluate the robustness of the results. In addition, interaction analysis will be applied for detecting the treatment discrepancies among different renal function groups. All statistical analyses will be performed using STATA software (version13, Statacorp, College Station, TX), and $P <.05$ indicate a statistically significant difference.

### 3. Discussion

CKD is associated with high risk of both stroke and major bleeding, and the assessment of balance between the risk of thromboembolic and bleeding events is essential in AF patients with CKD.\textsuperscript{2} Many CKD patients receive inadequate oral anticoagulation (OAC) in clinical setting due to worrying about bleeding while on OAC. Therefore, it is necessary to provide suitable anticoagulant therapy for AF patients accompanied with CKD. The updated clinical guidelines on the management of AF recommend NOACs, due to stable safety and efficacy, which is
favor for stroke prevention over warfarin in general NVAF patients.\[23\] However, there is no definite recommendation about the choice of warfarin or NOACs for stroke prevention in patients with CKD. Furthermore, the lack evidence for NCB property of NOACs versus warfarin for AF patients with varying degrees of renal function, leading to clinicians difficult to choose suitable OAC for these patients. For this reason, we will assess the efficacy, safety, and NCB of NOACs in AF patients with different stages of renal function.

Although CKD is not regarded as component factor of CHA2DS2-VASc score, it is closely associated with its risk factors, stages of renal function.\[2\] It is recognized that CKD is related to a suboptimal TTR in AF patients received warfarin therapy.\[4\] CKD might contribute to poor control of TTR via increasing risk of thromboembolism and bleeding.\[25\] In sub-analysis of previous studies, NOACs reduced the risk of SSE and major bleeding events in CKD patients.\[26–29\] For this issue, we will integrate included studies for powerful statistics to estimate NCB that incorporates the risk for SSE and major bleeding events of CKD patients receiving NOACs, and provide a greater NCB basis for the option on optimal anticoagulant therapy in AF patients.

Several limitations might be worth addressed in this study. First, the included trials may not be directly designed to evaluate the efficacy and safety of NOACs in patients with CKD. The differences in patient demographics, bleeding risk factors, concomitant drugs may be unsolved for further analysis. However, meta-regression analysis will be performed to assess available potential effect in baseline characteristics. Second, the statistical Singer’s method using 1.5 weighted index may not account for all clinical variables.\[16\] Thus, sensitivity analysis will be conducted using weighted factor of 1.0 and 2.0. Finally, the absence of head-to-head comparisons of NOACs in CKD patients, and limited number of included studies, may lead to an incomprehensive explanation, the result in this study may be applied only to limited scope.

4. Conclusions

The results will provide novel evidence for NOACs profile on efficacy, safety, and NCB compared to warfarin in CKD patients.

Author contributions

Conception and design: Zhi-Chun Gu and Nan-Nan Shen. Administrative support: Zhi-Chun Gu, An-Hua Wei, and Yue Wu. Provision of study materials or patients: Nan-Nan Shen and Xue-Min Zhang. Collection and assembly of data: Nan-Nan Shen, Xue-Min Zhang, and Ke-Jia Le. Data analysis and interpretation: Zhi-Chun Gu and Nan-Nan Shen. Manuscript writing: All authors. Final approval of manuscript: All authors. Conceptualization: Nan-Nan Shen, Xue-Min Zhang, Ke-Jia Le, An-Hua Wei, Yue Wu, Zhichun Gu.

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