Thrombosis Research 137 (2016) 46–52

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Safety of antithrombotic drugs in patients with atrial fibrillation and non-end-stage chronic kidney disease: Meta-analysis and systematic review

Ying Bai [a,1], Hui Chen [b,1], Yi Yang [a], Li Li [a], Xin-Yao Liu [a], Xu-Bo Shi [a], Chang-Sheng Ma [a,c,*]

[a] Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China
[b] School of Biomedical Engineering, Capital Medical University, Beijing, 100069, China
[c] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, National Clinical Research Center for Cardiovascular Diseases, Beijing, 100029, China

ARTICLE INFO

Article history:
Received 25 June 2015
Received in revised form 11 November 2015
Accepted 14 November 2015
Available online 21 November 2015

Keywords:
Atrial fibrillation
Non-end-stage chronic kidney disease
Major bleeding
Warfarin
Direct oral anticoagulants

ABSTRACT

Objective: To evaluate the safety of antithrombotic drugs used in patients with both atrial fibrillation (AF) and non-end-stage chronic kidney disease (NECKD).
Methods: A search was performed for studies on major bleeding outcomes in patients with concurrent AF and NECKD using Medline and Cochrane databases on 19th February, 2015. Fixed- or random-effects meta-analysis was adopted for evaluating pooled effect sizes according to whether heterogeneity existed.
Results: Twelve articles were included for analysis. Three studies evaluated AF patients who took warfarin vs. placebo/antiplatelet drugs in the presence of NECKD. No significant difference in major bleeding risk was observed according to the pooled analysis using the random-effects model (RR: 1.05, 95% CI: 0.74–1.36). The risk of a composite of major bleeding outcomes was reduced by 19% in patients randomized to direct oral anticoagulants (DOACs) compared to dose-adjusted warfarin from pooled data of three randomized controlled trials with regard to AF and NECKD (RR: 0.81, 95% CI: 0.75–0.88). This superiority of DOACs to warfarin maintained until the renal function was severely impaired.
Conclusions: In patients with AF and NECKD, no significant increase in the incidence of major bleeding outcomes was observed in warfarin use compared with placebo/antiplatelet drugs. DOACs reduced the risk of major bleeding by 19% compared to warfarin and further data-exploration indicated that the risk did not increase as renal function deteriorated during the renal status of mild to moderate impairment.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia which can lead to severe complications such as stroke [1]. The incidence of stroke can be reduced by antithrombotic drugs [2,3], including warfarin, aspirin and direct oral anticoagulants (DOACs) (i.e. dabigatran, apixaban and rivaroxaban). It is generally accepted that higher efficiency in prevention of stroke is often accompanied by higher risk of major bleeding [4], especially in patients with chronic kidney disease (CKD). CKD not only increases the risk of stroke [5], but also that of bleeding [6]. As a result, the use of anticoagulant drugs is placed in a dilemma in patients with both AF and CKD [7].

As major bleeding is shown to be associated with malignant prognosis in patients with AF [8], a lower risk of major bleeding is of great importance in choosing antithrombotic drugs in clinical practice. Therefore, it is prudent to assess the safety of antithrombotic drugs besides efficacy and net clinical benefits under conditions of CKD before making clinical decisions. Inconsistent results from recent studies on warfarin use [9,10] and limitations of DOACs metabolism in CKD [11,12,13] make it difficult to get a clear view of the association of various antithrombotic drugs with major bleeding risk in patients with AF and

Abbreviations: Atrial fibrillation, AF; Direct oral anticoagulants, DOACs; Chronic kidney disease, CKD; Non-end-stage chronic kidney disease, NECKD; Vitamin K-antagonist, VKA; Estimated glomerular filtration rate, eGFR; Chronic Kidney Disease Epidemiology Collaboration equation, CKD-PI; The Modification of Diet in Renal Disease study equation, MDRD; Hazard ratio, HR; Relative risk, RR; Confidence interval, CI; Randomized controlled trials, RCTs; Gastrointestinal bleeding, GIB; Time of therapy range, TTR; Randomized Evaluation of Long-term Anticoagulation Therapy, RE-LY; Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, ARISTOTLE; 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.

* Corresponding author at: Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing, 100730, China.
E-mail address: chshma@vip.sina.com (C.-S. Ma).
[1] The first two authors contribute equally to the article.

http://dx.doi.org/10.1016/j.thromres.2015.11.020
0049-3848/

CKD. This meta-analysis was performed to evaluate the risk of major bleeding in patients with concurrent AF and non-end-stage CKD (NECKD) by assembling evidence from recent published studies.

2. Methods

2.1. Literature search

A search using key words "chronic kidney disease" or "renal dysfunction" AND "atrial fibrillation" AND "VKA" or "Vitamin K-antagonist" or "bleeding" was performed in Medline and Cochrane databases on 19th February, 2015 by two investigators (Y.B. and Y.Y.) independently. The lists of the references from accessed full-texts were also reviewed for possible information related to this subject. Any disagreement between the two investigators was referred to a third reviewer (L.L.) for final decision.

2.2. Study selection and data extraction

Cross-sectional, cohort, randomized and observational studies assessing outcomes of bleeding were included in our analysis. To be included in this meta-analysis, studies should contain at least one piece of information from each item as follows:

(i). Types of interventions:

Warfarin use and warfarin non-use for AF anticoagulation in patients with NECKD.

Warfarin non-use included but were not restricted to placebo, antiplatelet drugs (i.e. aspirin, mono or dual antiplatelet therapy), aspirin only, aspirin plus fixed, low-dose warfarin and DOACs (i.e. dabigatran, apixaban and rivaroxaban).

(ii). Safety outcome measures:

1. Major bleeding complications, i.e. any fatal or non-fatal intracranial or major extracranial hemorrhage;
2. Intracranial hemorrhage, fatal or non-fatal;
3. Gastrointestinal hemorrhage, fatal or non-fatal;
4. Major extracranial hemorrhage, according to the definitions of the original study.

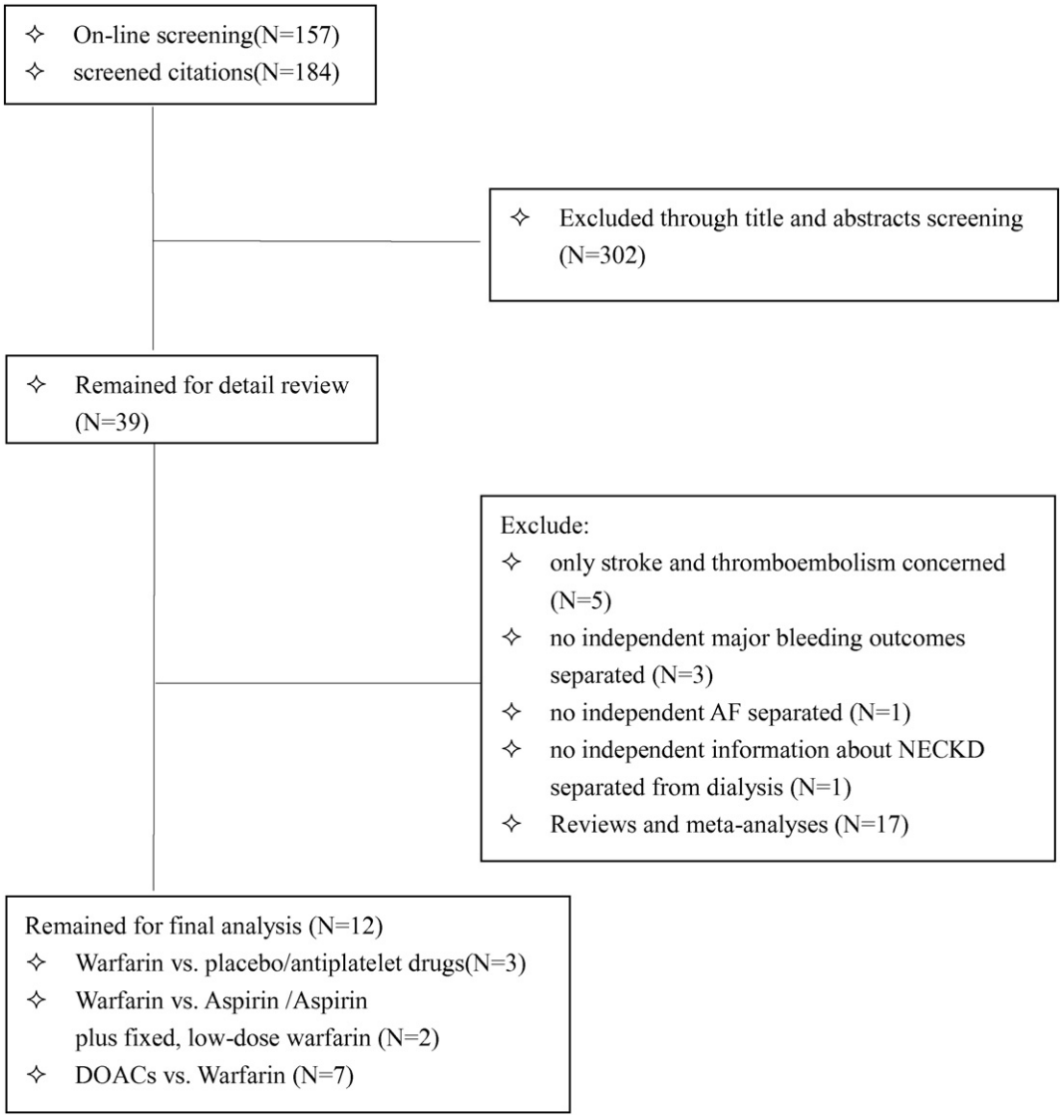

Fig. 1. Flowchart diagram illustrating study selection. AF, atrial fibrillation; NECKD, non-end-stage chronic kidney disease; DOACs, direct oral anticoagulants; N, number.