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SYSTEMATIC REVIEW

Efficacy and Safety of Direct Oral Anticoagulants vs Warfarin in Patients with Chronic Kidney Disease and Dialysis Patients: A Systematic Review and Meta-Analysis

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Abstract

Background and Objective Systematic reviews and meta-analyses of direct oral anticoagulants (DOACs) for patients with chronic kidney disease (CKD) or dialysis patients are lacking. We aimed to compare the efficacy and safety of DOACs and warfarin in patients with CKD requiring anticoagulation therapy.

Methods We performed a systematic review and meta-analysis of six randomized controlled trials and 19 observational studies, with the inclusion criteria being a comparative study between DOACs and warfarin in patients with CKD or dialysis patients from database inception until August 2020. The efficacy outcomes were stroke, systemic embolism (SE), or venous thromboembolism (VTE), and the safety outcome was major bleeding.

Results Compared with warfarin, DOACs significantly reduced the risk of stroke/SE/VTE by 22% (hazard ratio [HR] = 0.78, 95% confidence interval [CI] 0.64–0.95) and major bleeding by 17% (HR = 0.83, 95% CI 0.71–0.97). On comparing factor Xa inhibitors and dabigatran with warfarin separately, factor Xa inhibitors significantly reduced the risk of stroke/SE/VTE (HR = 0.78, 95% CI 0.62–0.98) and major bleeding (HR = 0.76, 95% CI 0.64–0.91) overall in patients. Comparing each DOACs with warfarin separately, apixaban was associated with a significantly better risk reduction of stroke/SE/VTE (25% risk reduction) and major bleeding (35% risk reduction) than warfarin. Compared with warfarin, DOACs significantly reduced the risk of stroke, SE, or VTE by 19% (HR = 0.81, 95% CI 0.68–0.97) in patients with CKD stage 3 and significantly lowered the risk of major bleeding by 31% (HR = 0.69, 95% CI 0.56–0.85) in patients with CKD stages 4–5.

Conclusions In pooled, analyzed randomized controlled trials and observational studies, DOACs were associated with better efficacy in early CKD, as well as similar efficacy and safety outcomes to warfarin in patients with CKD stages 4–5 or dialysis patients. The results of patients with CKD stages 4–5 and dialysis patients were from observational studies. Well-designed randomized controlled trials focused on DOAC use in patients with CKD and dialysis patients are needed.

PROSPERO register number: CRD42020150599, 6 February, 2020.

1 Introduction

The need for anticoagulation therapy is higher in patients with chronic kidney disease (CKD) than in the general population because the prevalence of atrial fibrillation (AF) increases with declining renal function [1–3]. Atrial fibrillation prevalence is <1% in the general population, 7–27% in patients with end-stage renal disease [4, 5], and 18–21% in non-dialysis patients with CKD [6, 7]. Atrial fibrillation is a well-known risk factor for thromboembolism [2], and CKD is independently associated with an increased stroke risk after adjusting for conventional risk factors [8–11]. Systematic reviews of numerous randomized controlled trials (RCTs) have shown that dose-adjusted warfarin reduces the risk of stroke in the general population with AF [12, 13]. However, the optimal antithrombotic treatment with warfarin in patients with CKD with AF remains unclear because patients with CKD are excluded in large-scale RCTs [14]. The current recommendations for warfarin use in patients with CKD with AF are mostly extrapolated from RCTs designed for the general population or based on observational studies and have demonstrated conflicting results [15, 16].

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Key Points

Direct oral anticoagulants had significantly better efficacy than warfarin in patients with chronic kidney disease stage 3.

The efficacy and safety profiles were similar in patients with chronic kidney disease stages 4–5 or dialysis patients.

Factor Xa inhibitors exhibited significantly better efficacy and safety profiles, especially apixaban when compared with warfarin.

Direct oral anticoagulants (DOACs) including direct thrombin (dabigatran) and factor Xa (apixaban, edoxaban, and rivaroxaban) inhibitors prevent stroke in the general population; these inhibitors do not require routine monitoring and are easy to use [17–21]. Compared with warfarin, DOACs achieved similar risk reductions for stroke and thromboembolism without increasing the risk of bleeding in patients with creatinine clearance (CrCl) of 30–49 mL/min and those with CrCl $\geq$ 50 mL/min [17–21]. These results were based on subgroup analyses of RCTs, but patients with advanced CKD with CrCl $<$ 25–30 mL/minor serum creatinine $>$ 2.5 mg/dL were excluded. Numerous observational studies and subgroup analyses of RCTs have been conducted to examine the efficacy and safety of DOACs in patients with CKD and end-stage renal disease. However, a systematic review and meta-analysis comparing DOACs with warfarin in patients with CKD and dialysis patients who require anticoagulation therapy are still lacking. Hence, our aim was to conduct a systematic review and meta-analysis to examine the efficacy and safety profile in patients with CKD and end-stage renal disease between DOACs and warfarin.

2 Methods

2.1 Study Design

We conducted a systematic review and meta-analysis comparing the efficacy and safety of DOACs and warfarin for patients with AF or venous thromboembolism (VTE). This systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [22] and The Cochrane Collaboration form [23].

2.2 Search Strategy and Eligibility Criteria

PubMed, Embase, and the Cochrane Library were searched for eligible articles from database inception until 31 August, 2020. Searches were performed using keywords and medical subject headings (MeSH) terms without language restrictions. The search keywords were based on the following strategy: "hemodialysis" or "renal dialysis" or "chronic renal insufficiency" or "kidney disease" or "renal insufficiency" or "end stage renal disease" and "dabigatran" or "edoxaban" or "apixaban" or "rivaroxaban" and "warfarin." Full details of the search strategies are available in Table S2 of the Electronic Supplementary Material [ESM]. The reference lists of relevant reports were manually searched to identify any missing relevant research articles or strategies.

2.3 Study Selection

All RCTs or observational studies were included if they reported (1) patients with CKD stages 3–5 or hemodialysis patients; (2) dabigatran, edoxaban, apixaban, or rivaroxaban and warfarin; and (3) stroke, systemic embolism (SE), VTE, or major bleeding. The exclusion criteria were: (1) patients with non-advanced CKD; (2) studies that did not compare dabigatran, edoxaban, apixaban, or rivaroxaban and warfarin, or studies of DOACs or warfarin alone as anticoagulants; and (3) studies without retrievable endpoints. The titles, abstracts, and contents were screened by two authors (YCS and HYC) to determine whether the studies met the inclusion criteria. The full texts of potentially relevant studies were retrieved and then assessed in more detail.

2.4 Data Extraction

Two reviewers (HYC and YCS) independently assessed the studies for eligibility and extracted the data using a standardized data extraction form. Disagreements were resolved through discussion with a third author (CCW). The following parameters were extracted from each study: general characteristics (first author, year of publication, study terms, study design, and country), patient characteristics (number of patients in each treatment arm; patient age; CHADS2, CHA2DS2-VASc score, or HAS-BLED score/bleeding index score [mean $\pm$ standard deviation or median (interquartile range)]; renal function/CKD stage; and international normalized ratio), characteristics of treatment regimen (dabigatran, edoxaban, apixaban, rivaroxaban, and warfarin and their dosage), efficacy, and safety (stroke, SE, or VTE and major bleeding). Any unpublished data indicated in the included studies were clarified by contacting the authors.

2.5 Quality Assessment

Quality assessment of these studies was performed using The Cochrane Collaboration's "Risk of Bias" tool 2.0 for all RCTs [24]. For each included trial, a judgment of bias was provided for each of the following domains: allocation, performance, follow-up, measurement, reported bias, and overall. The observational studies included in the meta-analysis were assessed for methodological quality using the Newcastle–Ottawa scale [25]. This scale assesses study selection (four items), comparability (two items), and ascertainment of exposure/outcome (three items). "High"-quality items were scored with a "star." A study was awarded a maximum of one star for each item within the selection and exposure/outcome categories, while a maximum of two stars was given for the comparability category. The maximum score was nine. A final score of ≥ 7 indicated high quality. These quality assessments were judged independently by two reviewers (WCC and HYC) and any conflict was discussed with the third reviewer (YCS).

2.6 Statistical Analysis

In the RCTs or observational studies, hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were extracted for stroke, SE, VTE, or major bleeding. If a multivariate analysis or propensity score matching was reported, an adjusted HR was used. For articles reporting only the total number of patients and event numbers in each group (DOACs vs warfarin), the HR was calculated from the risk ratio based on the methodology published by Parmar et al. [26] The inverse variance method was used to calculate overall HR and 95% CI [27]. Quantitative meta-analyses of pooled-effect estimates were calculated and were presented using forest plots. The outcomes were analyzed using the DerSimonian–Laird random-effects model to address potential high heterogeneity among the studies. Subgroup analyses were carried out according to the study characteristics to investigate the source of heterogeneity, which included study design (RCT and non-RCT), different DOACs, and CKD stage. Inter-study heterogeneity was measured using Cochran's Q test. Substantial statistical heterogeneity between studies was defined as a statistically significant χ^2 value ($p < 0.10$). I^2 values of 0–24.9%, 25–49.9%, 50–74%, and 75–100% denoted no, low, moderate, and high heterogeneity, respectively. Funnel plot analysis [28] and Egger's test [29] were performed to assess small study bias and/or publication bias. Statistical analysis was performed using Review Manager 5.3. [30] The results were considered statistically significant when the p value (two-sided) was < 0.05.

3 Results

3.1 Characteristic Information of Search Results

Through the search strategy for electronic databases, 1877 studies were identified. After reviewing the titles and abstracts, 1791 publications were either duplicates or irrelevant and were thus excluded. Out of 86 articles retrieved for full-text evaluation, we excluded 20 owing to an incorrect population or outcome, eight with inappropriate interventions, and 31 that were reviews, commentaries, editorials, or protocols. Therefore, six RCTs and 19 observational studies were included in the meta-analysis (Fig. 1), and all of these reported outcomes with stroke, SE, or VTE and major bleeding [31–55]. One of the RCTs was a pooled analysis from the RE-COVER and RECOVER II trials [37]. All eligible trials enrolled DOACs with dabigatran (seven), edoxaban (three), apixaban (13), or rivaroxaban (14) compared with warfarin in patients with CKD. Four studies were conducted in Asia. The remaining 21 studies were conducted in America and Europe. Three of these trials compared dabigatran and rivaroxaban with warfarin in the same trial [32, 38, 42]. Eight studies compared apixaban with warfarin [39, 44–46, 49, 50, 54, 55]. Six studies compared rivaroxaban with warfarin [34–36, 41, 52, 53]. Two studies compared dabigatran with warfarin [37, 40]. One study compared edoxaban with warfarin [31]. Three studies compared dabigatran, rivaroxaban, and apixaban with warfarin [43, 47, 48]. Meanwhile, two studies compared all DOACs with warfarin [33, 51]. The characteristics and measured effects of the 25 studies are summarized in Table S1 of the ESM. Five observational studies performed propensity score matching. Most studies involved AF. The mean or median CHADS2 or CHA2DS2-VASc score of enrolled participants was above 2 in 16 publications. Nine studies included HAS-BLED scores above 2. The enrolled studies included nine at CKD stage 3 and seven at CKD stages 4–5 for stroke/SE/VTE and major bleeding. Chronic kidney disease stage 5 with hemodialysis was noted in seven and nine studies for stroke/SE/VTE and major bleeding, respectively. Thirteen studies provided HR for stroke/SE/VTE, and six studies provided numbers for stroke/SE/VTE evaluation. For 14 out of 25 studies for major bleeding, HR data were shown. The quality of eligible RCTs and observational studies were assessed using the Cochrane Risk of Bias 2.0 tool and the Newcastle–Ottawa Scale, respectively (Table S3, Fig. S1A and S1B of the ESM). Allocation concealment was inadequate in one RCT [39] and there were some concerns in the remaining studies [31, 36, 37, 40, 41]. Reporting bias was found in two RCTs [37, 39]. All of the observational studies scored

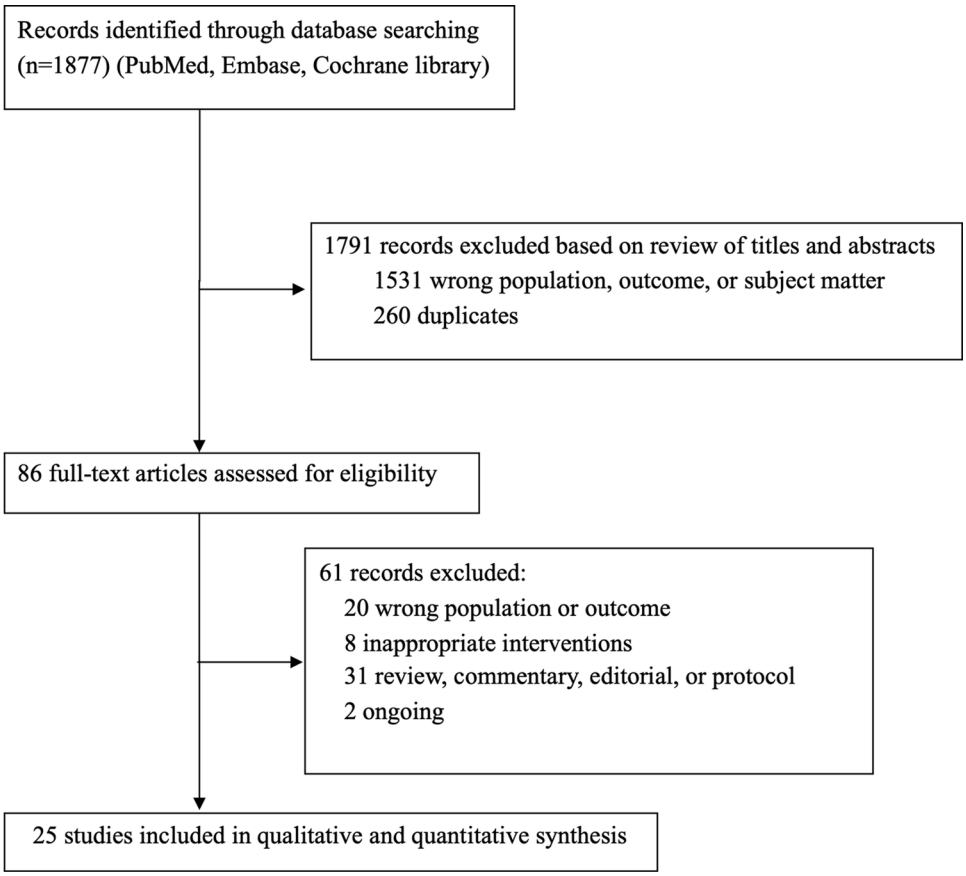


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart summarizing study identification and selection

from 2 to 8 on the Newcastle–Ottawa Scale criteria and were included in the quantitative analysis. Seven cohort studies were considered to be of high quality (Newcastle–Ottawa score ≥ 7) [32–34, 44, 47, 49, 52].

3.2 Effect on stroke, SE, or VTE and major bleeding

The DOAC group was significantly associated with a 22% lower risk of stroke, SE, or VTE than the warfarin group (HR 0.78, 95% CI 0.64–0.95) (Fig. 2a). The pooled estimated HR of the RCTs was 0.75 (95% CI 0.62–0.91), showing a significant difference in stroke, SE, or VTE between DOACs and warfarin. A similar reduction was seen in the observational studies but failed to achieve significance in the observational studies (HR = 0.78, 95% CI 0.59–1.03). The DOAC group was associated with a 17% reduction in major bleeding risk compared with the warfarin group (HR = 0.83, 95% CI 0.71–0.97). The HR for the subgroup analysis was 0.83 (95% CI 0.67–1.02) in the RCTs and 0.81 (95% CI 0.66–0.99) in the observational studies (Fig. 2b). There were nine studies analyzing the risk of intracranial hemorrhage between DOACs and VKA [31, 35, 36, 40, 41, 48, 52–54]. The DOAC group was significantly associated with a 50% reduction in intracranial hemorrhage risk compared with the warfarin group (HR = 0.50, 95% CI 0.33–0.77) (Fig. S2 of the ESM).

3.3 Subgroup Analysis

3.3.1 By DOAC Type

The subgroup analysis of DOAC type included non-dabigatran DOACs of edoxaban, rivaroxaban, apixaban, and dabigatran [31, 32, 34–37, 39–41, 44, 46, 49, 50, 52–55]. Compared with warfarin, non-dabigatran DOACs were significantly associated with a 24% reduced risk of stroke, SE, or VTE compared with warfarin, and a similar reduction was seen in the dabigatran vs warfarin group but failed to achieve significance (dabigatran: HR = 0.75, 95% CI 0.26–2.18, I^2 = 83%; non-dabigatran DOACs: HR = 0.78, 95% CI 0.62–0.98, I^2 = 44%; subgroup differences: p = 0.95) (Table 1, Fig. S3 of the ESM). In the subgroup analysis of major bleeding, non-dabigatran DOACs was shown to significantly reduce major bleeding (non-dabigatran DOACs: HR = 0.76, 95% CI 0.64–0.91, I^2 = 62%). The comparison to dabigatran showed no significant difference in the pooled analysis of the studies [31, 32, 34, 36–41, 44–46, 49–55] (dabigatran: HR = 1.21, 95% CI 0.99–1.49, I^2 = 49%) (Table 1, Fig. S4 of the ESM). However, in the

pooled analysis, a significant difference across subgroups of patients by DOAC type was noted for major bleeding (test for subgroup differences: $p < 0.001$, $I^2 = 91.6\%$ between non-dabigatran DOACs and dabigatran) (Fig. S4 of the ESM). On comparing four DOACs with warfarin separately on efficacy and safety outcomes, apixaban was significantly associated with a 25% reduced risk of stroke/SE/VTE compared with warfarin (HR = 0.75, 95% CI 0.57–0.98) (Fig. S5 of the ESM), as well as a significantly reduced 35% risk of major bleeding compared with warfarin (HR = 0.65, 95% CI 0.46–0.91) (Fig. S6 of the ESM).

3.3.2 By CKD Stage

Subgroup analyses were also conducted according to CKD stage, particularly on CKD stage 3 [31, 34, 36, 37, 39, 40, 42, 47], which showed a significant association with a reduced risk of stroke, SE, or VTE. Chronic kidney disease stages 4–5 [32, 33, 43, 44, 46, 49, 50, 52] with hemodialysis rendered this association not significant (CKD stage 3: HR = 0.81, 95% CI 0.68–0.97, $I^2 = 22\%$; CKD stages 4–5: HR = 0.77, 95% CI 0.45–1.32, $I^2 = 37\%$; and CKD stage 5 with hemodialysis: HR = 0.92, 95% CI 0.54–1.58, $I^2 = 74\%$; subgroup differences: $p = 0.88$) (Table 2, Fig. S7 of the ESM). In CKD stages 4–5, DOACs significantly reduced the risk of major bleeding. In CKD stage 3, there was a marginally significant effect (CKD stage 3: HR = 0.85, 95% CI 0.69–1.05, $I^2 = 67\%$; CKD stages 4–5: HR = 0.69, 95% CI 0.56–0.85, $I^2 = 0\%$; and CKD stage 5 with hemodialysis: HR = 0.82, 95% CI 0.56–1.22, $I^2 = 86\%$; subgroup differences: $p = 0.34$) (Table 2, Fig. S8 of the ESM).

3.3.3 By Population Type

Subgroup analyses were also conducted according to the population. Direct oral anticoagulants were shown to significantly reduce the risk of VTE compared with warfarin in the VTE population (VTE population: HR = 0.14, 95% CI 0.04–0.54, $I^2 = 0\%$), and had a trend to reduce stroke or SE risk in the AF population more than warfarin (HR = 0.83, 95% CI 0.68–1.01, $I^2 = 54\%$; subgroup differences: $p = 0.01$) (Table 1). Furthermore, DOACs were significantly associated with a 20% reduction in major bleeding risk compared with warfarin in the AF population (HR = 0.80, 95% CI 0.67–0.97), and the risks of major bleeding were similar between DOACs and warfarin in the VTE population (HR = 0.56, 95% CI 0.11–2.88) (Table 1).

3.4 Publication Bias

According to Egger's test, there was no significant evidence of publication bias for stroke, SE, or VTE and for major bleeding ($p = 0.412$ and $p = 0.146$, respectively).

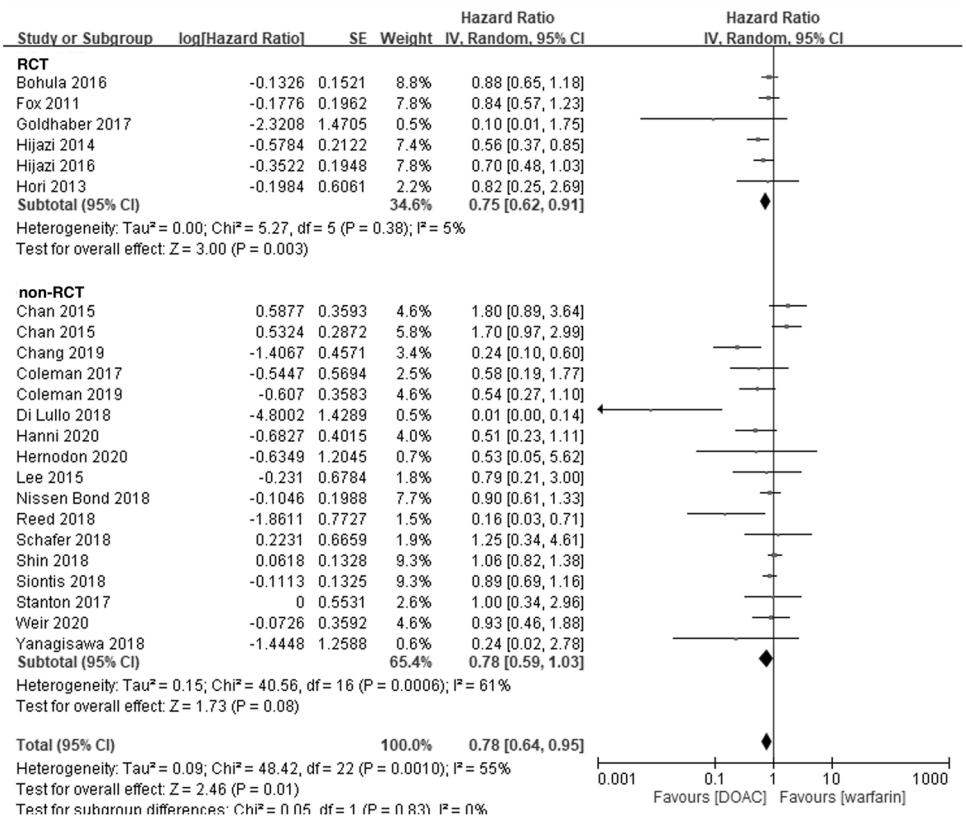
4 Discussion

Our systematic review and meta-analysis utilized six RCTs and 19 observational studies to provide a comprehensive comparison of the efficacy and safety between DOACs and warfarin in patients with CKD. Compared with warfarin, DOACs significantly reduced the stroke/SE/VTE risk by 22% and major bleeding risk by 17% in all patients with CKD. Factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) were associated with a significantly better prevention of stroke/SE/VTE (22% risk reduction) and major bleeding (24% risk reduction) than warfarin. Comparing each DOAC with warfarin separately, apixaban was associated with a significantly better risk reduction in stroke/SE/VTE (25% risk reduction) and major bleeding (35% risk reduction) than warfarin. Considering the prevention of stroke or thromboembolism in different CKD stages, DOACs exhibited significantly better efficacy than warfarin in patients with CKD stage 3, as well as similar efficacy in patients with CKD stages 4–5 or dialysis patients. As for major bleeding, DOACs showed significantly better safety profiles than warfarin in patients with CKD stages 4–5, as well as similar safety in patients with CKD stage 3 or dialysis patients. The results of patients with CKD stages 4–5 and dialysis patients were mainly retrieved from observational studies, and further well-designed large-scale RCTs will be needed.

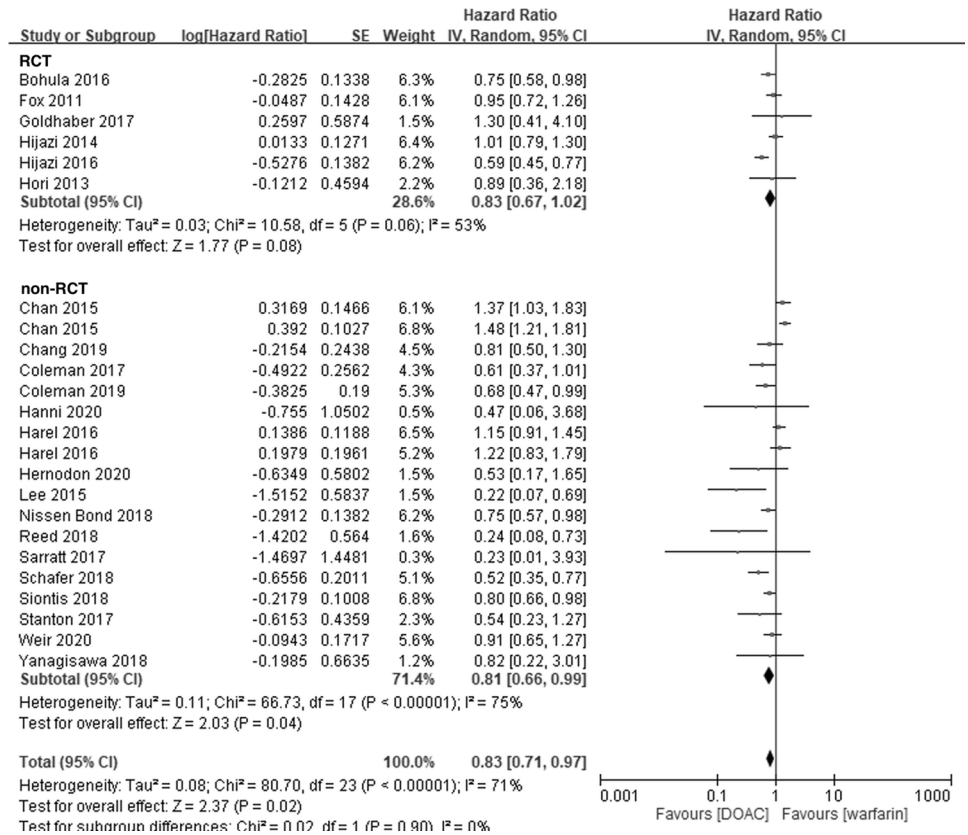
The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline suggests that warfarin use is reasonable in patients with CrCl < 15 mL/min or those receiving dialysis with nonvalvular AF and CHA_2DS_2-VASc scores ≥ 2 [56]. However, warfarin use in patients with CKD raises the concern of increasing the risk of ectopic/vascular calcification, aortic valve calcification, impaired regulation of bone mineralization, and lower bone density [57–59]. Therefore, many patients with CKD who meet the anticoagulation criteria do not receive anticoagulation therapy [60]. Our systematic review and meta-analysis of RCTs and observational studies of real-world clinical practice demonstrates the efficacy and safety of DOACs in every category of CKD, when compared with warfarin. Furthermore, DOAC use can avoid the unwanted adverse effects induced by warfarin. It is reasonable that DOAC use in patients with CKD is substantial and increasing [61].

Patients with advanced CKD and dialysis patients are prone to uremic bleeding due to platelet dysfunction. The involvement of renal clearance in DOAC metabolism varies (dabigatran, 80%; edoxaban, 50%; rivaroxaban, 33%; apixaban, 27%) [61]. The DOAC elimination half-lives are also different from each other (dabigatran, 12–17 h; edoxaban, 9–11 h; rivaroxaban, 11–13 h; apixaban, 12 hours) [62]. Fifty to

a


Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
Hazard Ratio IV, Random, 95% CI
RCT
Bohula 2016 -0.1326 0.1521 8.8% 0.88 [0.65, 1.18]
Fox 2011 -0.1776 0.1962 7.8% 0.84 [0.57, 1.23]
Goldhaber 2017 -2.3208 1.4705 0.5% 0.10 [0.01, 1.75]
Hijazi 2014 -0.5784 0.2122 7.4% 0.56 [0.37, 0.85]
Hijazi 2016 -0.3522 0.1948 7.8% 0.70 [0.48, 1.03]
Hori 2013 -0.1984 0.6061 2.2% 0.82 [0.25, 2.69]
Subtotal (95% CI) 34.6% 0.75 [0.62, 0.91]
Heterogeneity: Tau² = 0.00; Chi² = 5.27, df = 5 (P = 0.38); I² = 5%
Test for overall effect: Z = 3.00 (P = 0.003)
non-RCT
Chan 2015 0.5877 0.3593 4.6% 1.80 [0.89, 3.64]
Chan 2015 0.5324 0.2872 5.8% 1.70 [0.97, 2.99]
Chang 2019 -1.4067 0.4571 3.4% 0.24 [0.10, 0.60]
Coleman 2017 -0.5447 0.5694 2.5% 0.58 [0.19, 1.77]
Coleman 2019 -0.607 0.3583 4.6% 0.54 [0.27, 1.10]
Di Lullo 2018 -4.8002 1.4289 0.5% 0.01 [0.00, 0.14]
Hanni 2020 -0.6827 0.4015 4.0% 0.51 [0.23, 1.11]
Hernodon 2020 -0.6349 1.2045 0.7% 0.53 [0.05, 5.62]
Lee 2015 -0.231 0.6784 1.8% 0.79 [0.21, 3.00]
Nissen Bond 2018 -0.1046 0.1988 7.7% 0.90 [0.61, 1.33]
Reed 2018 -1.8611 0.7727 1.5% 0.16 [0.03, 0.71]
Schafer 2018 0.2231 0.6659 1.9% 1.25 [0.34, 4.61]
Shin 2018 0.0618 0.1328 9.3% 1.06 [0.82, 1.38]
Siontis 2018 -0.1113 0.1325 9.3% 0.89 [0.69, 1.16]
Stanton 2017 0 0.5531 2.6% 1.00 [0.34, 2.96]
Weir 2020 -0.0726 0.3592 4.6% 0.93 [0.46, 1.88]
Yanagisawa 2018 -1.4448 1.2588 0.6% 0.24 [0.02, 2.78]
Subtotal (95% CI) 65.4% 0.78 [0.59, 1.03]
Heterogeneity: Tau² = 0.15; Chi² = 40.56, df = 16 (P = 0.0006); I² = 61%
Test for overall effect: Z = 1.73 (P = 0.08)
Total (95% CI) 100.0% 0.78 [0.64, 0.95]
Heterogeneity: Tau² = 0.09; Chi² = 48.42, df = 22 (P = 0.0010); I² = 55%
Test for overall effect: Z = 2.46 (P = 0.01)
0.001 0.1 1 10 1000
Favours [DOAC] Favours [warfarin]

b


Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
Hazard Ratio IV, Random, 95% CI
RCT
Bohula 2016 -0.2825 0.1338 6.3% 0.75 [0.58, 0.98]
Fox 2011 -0.0487 0.1428 6.1% 0.95 [0.72, 1.26]
Goldhaber 2017 0.2597 0.5874 1.5% 1.30 [0.41, 4.10]
Hijazi 2014 0.0133 0.1271 6.4% 1.01 [0.79, 1.30]
Hijazi 2016 -0.5276 0.1382 6.2% 0.59 [0.45, 0.77]
Hori 2013 -0.1212 0.4594 2.2% 0.89 [0.36, 2.18]
Subtotal (95% CI) 28.6% 0.83 [0.67, 1.02]
Heterogeneity: Tau² = 0.03; Chi² = 10.58, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 1.77 (P = 0.08)
non-RCT
Chan 2015 0.3169 0.1466 6.1% 1.37 [1.03, 1.83]
Chan 2015 0.392 0.1027 6.8% 1.48 [1.21, 1.81]
Chang 2019 -0.2154 0.2438 4.5% 0.81 [0.50, 1.30]
Coleman 2017 -0.4922 0.2562 4.3% 0.61 [0.37, 1.01]
Coleman 2019 -0.3825 0.19 5.3% 0.68 [0.47, 0.99]
Hanni 2020 -0.755 1.0502 0.5% 0.47 [0.06, 3.68]
Harel 2016 0.1386 0.1188 6.5% 1.15 [0.91, 1.45]
Harel 2016 0.1979 0.1961 5.2% 1.22 [0.83, 1.79]
Hernodon 2020 -0.6349 0.5802 1.5% 0.53 [0.17, 1.65]
Lee 2015 -1.5152 0.5837 1.5% 0.22 [0.07, 0.69]
Nissen Bond 2018 -0.2912 0.1382 6.2% 0.75 [0.57, 0.98]
Reed 2018 -1.4202 0.564 1.6% 0.24 [0.08, 0.73]
Sarratt 2017 -1.4697 1.4481 0.3% 0.23 [0.01, 3.93]
Schafer 2018 -0.6556 0.2011 5.1% 0.52 [0.35, 0.77]
Siontis 2018 -0.2179 0.1008 6.8% 0.80 [0.66, 0.98]
Stanton 2017 -0.6153 0.4359 2.3% 0.54 [0.23, 1.27]
Weir 2020 -0.0943 0.1717 5.6% 0.91 [0.65, 1.27]
Yanagisawa 2018 -0.1985 0.6635 1.2% 0.82 [0.22, 3.01]
Subtotal (95% CI) 71.4% 0.81 [0.66, 0.99]
Heterogeneity: Tau² = 0.11; Chi² = 66.73, df = 17 (P < 0.00001); I² = 75%
Test for overall effect: Z = 2.03 (P = 0.04)
Total (95% CI) 100.0% 0.83 [0.71, 0.97]
Heterogeneity: Tau² = 0.08; Chi² = 80.70, df = 23 (P < 0.00001); I² = 71%
Test for overall effect: Z = 2.37 (P = 0.02)
0.001 0.1 1 10 1000
Favours [DOAC] Favours [warfarin]

◂**Fig. 2** Forest plot of (**a**) stroke, systemic embolism, or venous thromboembolism results among users of direct oral anticoagulants (DOACs) vs warfarin. In the non-randomized controlled trial (RCT) subgroup analysis, "Chan 2015" presented the results of two comparisons (rivaroxaban vs warfarin, rate ratio 1.8; dabigatran vs warfarin, rate ratio 1.7). Forest plot of (**b**) major bleeding results among users of DOACs vs warfarin. In the non-RCT subgroup analysis, "Chan 2015" presented the results of two comparisons (rivaroxaban vs warfarin, hazard ratio 1.37; dabigatran vs warfarin, hazard ratio 1.48), and "Harel 2016" also presented the results of two comparisons (dabigatran vs warfarin, odd ratio 1.15; rivaroxaban vs warfarin, odd ratio 1.22). *CI* confidence interval, *SE* systemic error

sixty percent of dabigatran can be removed by 4 h of hemodialysis, while < 10% of other DOACs can be removed (apixaban, 7%; rivaroxaban, < 1%; edoxaban, 9%). Well-planned multi-dose pharmacokinetic studies and further RCTs to validate pharmacokinetic results in patients with advanced CKD and dialysis patients are lacking. A major bleeding risk is the most concerning issue when using DOACs in patients with CKD. Real-world practices found in the Fresenius database (consisting of 102,504 patients with AF with advanced CKD and 140,918 patients with AF receiving dialysis) have demonstrated an increased use of apixaban (10.4%) and rivaroxaban (9.5%), and a decreased use of dabigatran (3.5%) in patients with advanced CKD as of October 2015 [61]. In dialysis patients, apixaban is used far more frequently (10.5%) than the other three DOACs. Our subgroup analysis demonstrated a significantly better non-dabigatran DOAC efficacy and safety profile, especially with apixaban when comparing with warfarin. Therefore, our results support real-world practices.

Our study has five major limitations. First, there was no standard dose-adjusted protocol in every included study, and the dose of DOACs in the same category of patients with CKD was not exactly the same. However, well-designed multi-dose pharmacokinetic studies and RCTs for the CKD population are lacking. Consequently, a standard dose-adjusted protocol is difficult to establish. Second, the included study population was not purely patients with nonvalvular AF, and we analyzed stroke, SE, and VTE together as the same efficacy outcome, and may have introduced bias because of the different pathophysiology of SE and VTE. However, according to a 20-year population-based Danish cohort (25,199 patients), patients with deep vein thrombosis had a relative risk of 2.19 for stroke, whereas patients with pulmonary embolism had a relative risk of 2.93 for stroke [62]. It is reasonable to include these studies because patients with VTE have an increased risk of stroke and fulfill the DOAC indication. To clarify the limitation, we analyzed the VTE and AF populations on SE and VTE outcome separately. There were two studies reporting the VTE population and 19 studies reporting the AF population. In the pooled 2 analysis with the reporting VTE population (237 patients with VTE in Goldhaber et al. [37] and 66 patients with VTE in Reed et al. [44]), DOACs were significantly associated with reducing the risk of VTE compared with warfarin. In the pooled 17 analysis with a reporting AF population, DOACs tended to reduce the stroke or SE risk in the AF population more than warfarin. Third, we included post hoc analyses of RCTs and observational studies, and these could have led to bias. To overcome the inherent bias, we utilized the corresponding HR value to present our outcomes. Fourth, not all the studies used the Cockcroft–Gault equation for CrCl to define renal function; some studies used the CKD-EPI equation. As a result, we grouped the patients according to the nearest CrCl threshold into patients with CKD stages 3 and 4–5 without dialysis and dialysis patients. This might have introduced sampling bias. Fifth, we used HR to present our outcomes. Because HR may change over time, and with a built-in selection bias, the use of HR for a causal relationship interpretation is not straightforward, even without unmeasured confounding factors, measurement error, and model misspecification. Sixth, the results of patients with CKD stages 4–5 and dialysis patients were mainly retrieved from observational studies, and further well-designed RCTs are needed to better clarify the efficacy and safety of DOAC use in patients with CKD.

5 Conclusions

Our systematic review and meta-analysis showed that compared to warfarin, DOACs had significantly better efficacy in patients with early-stage CKD. The efficacy and safety profiles were however similar in patients with CKD stages 4–5 or dialysis patients. Factor Xa inhibitors exhibited significantly better efficacy and safety profiles, especially apixaban when compared with warfarin.

Table 1 Risk of stroke/SE/VTE and major bleeding between DOACs and warfarin by different stratification

Group variable	Subgroups	Number of studies	Adjust HR (95% CI)	Test for subgroup differences (p value; I^2)
Stroke or SE or VTE				
All studies		25	0.78 (0.64–0.95)	$I^2 = 55\%$
Study type				
	RCT	6	0.75 (0.62–0.91)	$I^2 = 5\%$
	Non-RCT	17	0.78 (0.59–1.03)	$I^2 = 61\%$
DOAC type			0.78 (0.62–0.98)	$p = 0.95$
	Non-dabigatran DOACs (edoxaban, rivaroxaban, apixaban)	15	0.78 (0.62–0.98)	$I^2 = 44\%$
	Dabigatran	3	0.75 (0.26–2.18)	$I^2 = 83\%$
Population type				$p = 0.01$
	VTE	2	0.14 (0.04–0.54)	$I^2 = 0\%$
	AF	18	0.83 (0.68–1.01)	$I^2 = 54\%$
Major bleeding				
All studies		25	0.83 (0.71–0.97)	$I^2 = 71\%$
Study type				
	RCT	6	0.83 (0.67–1.02)	$I^2 = 53\%$
	Non-RCT	18	0.81 (0.66–0.99)	$I^2 = 75\%$
DOAC type			0.84 (0.71–1.00)	$p < 0.001$
	Non-dabigatran DOACs (edoxaban, rivaroxaban, apixaban)	16	0.76 (0.64–0.91)	$I^2 = 62\%$
	Dabigatran	4	1.21 (0.99–1.49)	$I^2 = 49\%$
Population type				$p = 0.66$
	VTE	2	0.56 (0.11–2.88)	$I^2 = 77\%$
	AF	16	0.80 (0.67–0.97)	$I^2 = 77\%$

CI confidence interval, *CKD* chronic kidney disease, *DOACs* direct oral anticoagulants, *HR* hazard ratio, *RCT* randomized controlled trial, *SE* systemic embolism, *VTE* venous thromboembolism

Table 2 Risk of stroke/SE/VTE and major bleeding between DOACs and warfarin by CKD stage

Group variable	Subgroups	Number of studies	Adjust HR (95% CI)	Test for subgroup differences (p value; I^2)
Stroke or SE or VTE				
All studies		25	0.83(0.67–1.03)	$I^2 = 60\%$
CKD stage			0.84 (0.70–1.00)	$p = 0.88$
	Stage 3	9	0.81(0.68–0.97)	$I^2 = 22\%$
	Stages 4–5	4	0.77 (0.45–1.32)	$I^2 = 37\%$
	Stage 5 with HD	5	0.92 (0.54–1.58)	$I^2 = 74\%$
Major bleeding				
All studies		25	0.83 (0.71–0.98)	$I^2 = 72\%$
CKD stage			0.81 (0.68–0.96)	$p = 0.34$
	Stage 3	10	0.85 (0.69–1.05)	$I^2 = 67\%$
	Stages 4–5	5	0.69 (0.56–0.85)	$I^2 = 0\%$
	Stage 5 with HD	7	0.82 (0.56–1.22)	$I^2 = 86\%$

CI confidence interval, *CKD* chronic kidney disease, *DOACs* direct oral anticoagulants, *HD* hemodialysis, *HR* hazard ratio, *RCT* randomized controlled trial, *SE* systemic embolism, *VTE* venous thromboembolism

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Declarations

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Conflict of interest Hsin-Yu Chen, Shih-Hsiang Ou, Chien-Wei Huang, Po-Tsang Lee, Kang-Ju Chou, Pei-Chin Lin, and Yi-Chia Su have no conflicts of interest that are directly relevant to the content of this article.

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Author contributions H-YC was involved in the design of the study, extraction of the data, statistical analyses, interpretation of the results, and drafting and revising the manuscript. Y-CS was involved in the design of the study, extraction of the data, and revising the manuscript. S-HO and C-WH were involved in the interpretation of the results and revising the manuscript. P-TL was involved in the design of the study, interpretation of the results, and revising the manuscript. K-JC was involved in the interpretation of the results and revising the manuscript. P-CL was involved in the design of the study, interpretation of the results, and drafting and revising the manuscript. P-CL is the guarantor of the manuscript. She accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. P-CL attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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