CHEST

Major Bleeding and Hemorrhagic Stroke With Direct Oral Anticoagulants in Patients With Renal Failure

Systematic Review and Meta-Analysis of Randomized Trials

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BACKGROUND: Direct oral anticoagulants (DOACs) are used as an alternative for traditional antithrombotic therapy. However, the safety profile of DOACs in patients with renal failure (RF) has not been determined.

METHODS: A systematic review was performed assessing the reported safety of DOACs compared with vitamin K antagonists (VKAs) in patients with RF and estimated creatinine clearance (eCrCL) < 50 mL/min and eCrCL 50 to 80 mL/min. MEDLINE, EMBASE, Cochrane, and the Clinical Trials Registry (ClinicalTrials.gov) were searched for randomized clinical trials up to November 2015. The data were pooled by using both traditional frequentist and Bayesian random effects models.

RESULTS: Nine trials met the inclusion criteria. Among 94,897 participants, 54,667 (58%) had RF. Compared with VKAs, DOACs were associated with a significantly decreased risk for major bleeding in patients with eCrCL 50 to 80 mL/min (risk ratio, 0.87 [95% CI, 0.81-0.93]) and a nonsignificant decrease in the risk for major bleeding in patients with eCrCL < 50 mL/min (risk ratio, 0.83 [95% CI, 0.68-1.02]); there was evidence of significant heterogeneity. Indirect comparisons, using Bayesian network analysis, indicated that apixaban was associated with a decreased rate of major bleeding compared with other DOACs in patients with eCrCL < 50 mL/min. DOACs were associated with a significant decrease in the risk for hemorrhagic stroke compared with VKAs in patients with eCrCL < 50 mL/min and 50 to 80 mL/min.

CONCLUSIONS: As a class, DOACs are associated with a reduced risk for hemorrhagic stroke compared with VKAs in patients with RF. However, DOACs may differ from each other in their relative risk for major bleeding in patients with eCrCL < 50 mL/min.

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KEY WORDS: antithrombotic therapy; atrial fibrillation; DVT; pulmonary embolism; stroke

ABBREVIATIONS: AF = atrial fibrillation; CrI = credible interval; DOAC = direct oral anticoagulant; FDA = US Food and Drug Administration; eCrCL = estimated creatinine clearance; RCT = randomized clinical trial; RF = renal failure; RR = relative risk; TTR = time in therapeutic range; VKA = vitamin K antagonist

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Patients with renal failure (RF) experience a state that both predisposes them to a higher risk for thromboembolism and to an increased tendency for bleeding.[1] However, anticoagulant therapy is often indicated when patients with RF develop atrial fibrillation (AF) or VTE.[2-5]

Recently, direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban, and edoxaban, have emerged as alternatives to vitamin K antagonists (VKAs) for the prevention of VTE, or systemic emboli and stroke, in patients with an increased risk of VTE or AF. Compared with traditional VKA treatment, DOAC treatment is associated with a more predictable dose-response relationship, fewer food and drug interactions, shorter plasma half-lives, and an improved efficacy-to-safety ratio.[6] The improved safety of the DOACs has been highlighted with respect to their reduced risk for intracranial hemorrhage, as reported in Phase III trials of DOACs.[7-9] However, uncertainty exists regarding the clinical use of DOACs in patients with RF.

Current clinical practice guidelines do not generally differentiate between the different DOACs in their recommendations. However, DOACs do differ in terms of their mechanism of action and pharmacokinetics. All DOACs have some degree of renal excretion, with the highest levels seen for dabigatran (80%), followed by edoxaban (50%), rivaroxaban (35%), and apixaban (27%).[10-14] Patients with estimated creatinine clearance (eCrCL) $<$ 30 mL/min for rivaroxaban, edoxaban, and dabigatran, and eCrCL $<$ 25 mL/min for apixaban, were excluded from the Phase III trials.[15-23] Consequently, clinical practice guidelines call for careful use of DOACs in patients with RF and include recommendations for renal function monitoring, dose adjustment, and restricted use of these agents in patients with severe RF.[24,25] Because the data regarding the safety of DOACs in patients with RF are limited, it is unclear to what degree their use should be endorsed in patients with RF.

In light of the sparse data regarding use of DOACs in RF, we performed a systematic review and meta-analysis to summarize and evaluate the safety of DOACs in patients with RF. Specifically, we evaluated whether DOACs lower the risk for major bleeding and for hemorrhagic stroke, compared with VKAs, in patients with RF.

Materials and Methods

Data Sources and Searches

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses framework guidelines.[26] The systematic review was performed by using MEDLINE, EMBASE, and Cochrane through November 2015 to identify all published randomized clinical trials (RCTs) involving the comparison of DOACs for nonvalvular AF or VTE treatment vs standard care. Relevant studies were identified by using the following search terms: controlled clinical trial, CT, Phase III trials, apixaban, rivaroxaban, dabigatran, edoxaban, NOAC, and new oral anticoagulant. We subsequently searched and evaluated published systematic reviews, online resources, conference abstracts, and ClinicalTrials.gov to ensure identification of all published and unpublished studies. No language or date restrictions were applied. The protocol is documented online in the PROSPERO registry (CRD42014013730). Because this study was a review and meta-analysis, no internal review board approval was required.

Study Selection

Two investigators (B. H. R. and A. Perlman) identified and extracted articles independently for potential inclusion. Disagreements were resolved by consensus. The degree of RF was defined in accordance with the criteria used by the included trials, based on the following grouping: eCrCL $<$ 50 mL/min and eCrCL 50 to 80 mL/min. Although patients with eCrCL $<$ 30 or 25 mL/min were formally excluded from these trials, a few of these trials have reported on inclusion of such patients (121 patients in the Effective Anticoagulation With Factor Xa in Next Generation Treatment of Atrial Fibrillation [ENGAGE AF],[27] 77 in the Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY],[14] 270 in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE],[11] and eight in 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] study,[10] a total of 476 patients).

The primary endpoint of the present analysis was defined as intracranial hemorrhage and major bleeding or, when reported, the combination of major bleeding with clinically relevant nonmajor bleeding.[16-18,22,28]

Data Extraction and Quality Assessment

Two team members extracted relevant data from each article. Data for outcomes of interest were also extracted from Drugs@FDA, the open-access data website of the US Food and Drug Administration (FDA). Study quality was assessed by using The Cochrane Collaboration's tool for assessing risk of bias in RCTs.[29]

Selection Criteria

The following screening criteria were applied to determine qualitative eligibility: RCTs of adults comparing dabigatran etexilate, rivaroxaban, apixaban or edoxaban vs active control for nonvalvular AF or VTE. All RCTs that reported safety data according to the degree of renal impairment were included. We excluded trials of DOACs for

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other indications, pharmacokinetic studies in healthy adults, studies using placebo as comparator, reviews, case reports, nonrandomized trials, and observational studies.

Data Synthesis and Analysis

Traditional (frequentist method) analyses were performed by using RevMan version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration). We excluded from the analysis any data regarding edoxaban 30/15 mg from the ENGAGE AF study[16] because this dosage is not registered in the FDA or in Europe.

The Mantel-Haenszel fixed effect and random effect pooled risk ratios were calculated, as were the corresponding 95% CIs, to summarize the results overall and within subgroups for DOAC recipients vs comparators. P values for statistically significant heterogeneity was set at $< .05$, and I^2 was calculated to assess the degree of heterogeneity. For $I^2 > 50\%$, the Mantel-Haenszel random effect was used for analysis.

To assess differences between DOACs, Bayesian network meta-analyses were used for all outcomes. The different treatment strategies were treated as separate nodes (VKA-dabigatran, VKA-rivaroxaban, VKA-apixaban, and VKA-edoxaban). All network meta-analyses were constructed by using NetMetaXL.[30] Hazard ratios and 95% credible intervals (CrIs) were modeled with the use of Markov chain Monte Carlo methods. Network meta-analyses with vague priors, or noninformative priors, were conducted for the analyses. We checked and confirmed convergence after a 10,000-simulation burn-in phase.

Analyses were performed by using WinBUGS version 1.4.3 (MRC Biostatistics Unit). Sensitivity analyses were performed for variation in study duration treatment effect.

Results

A systematic search was conducted from October 2013 to November 2015. A total of 1,297 citations met the initial search criteria, and 23 articles met the inclusion criteria. Thirteen of these articles lacked information about safety in RF; these included the Dabigatran vs Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER) studies[31,32] and studies by Weitz et al,[33] Chung et al,[34] and Yamashita et al.[35] The Apixaban vs Acetylsalicylic Acid to Prevent Strokes (AVERROES) study was excluded from the final meta-analyses because it was the only study that used an antiplatelet medication (aspirin), and not VKA, as the comparator.[36] Nine trials were thus included in the final analyses (Fig 1).[15-23]

The conventional comparator in these studies was warfarin or subcutaneous enoxaparin followed by warfarin. The nine studies included 94,879 patients, 40,230 with normal renal function, 40,681 with eCrCL 50 to 80 mL/min, and 13,996 with eCrCL < 50 mL/min. Quality assessment is summarized in e-Table 1; the overall risk of bias among the included studies was low. Trials were all funded by pharmaceutical industry sources. The follow-up period ranged from 0.25 to 2.8 years. The major characteristics of the included trials are presented in Table 1. Patients with eCrCL < 30 mL/min for rivaroxaban, edoxaban, and dabigatran, and eCrCL < 25 mL/min for apixaban, were excluded from the RCTs. However, some of the studies reportedly included a small number of patients with eCrCL < 30 mL/min (476 patients).[11,10,14,27] The analysis of patients with eCrCL < 50 mL/min therefore includes some patients with eCrCL < 30 mL/min.

Major Bleeding

DOACs were associated with a decreased risk for major bleeding compared with VKAs in patients with eCrCL 50 to 80 mL/min (relative risk [RR], 0.87 [95% CI, 0.81-0.93]; $P = .0001$; $I^2 = 0\%$). In subgroup analyses, this association was significant only for apixaban and edoxaban (e-Fig 1A).

DOACs were associated with a nonstatistically significant decreased risk for major bleeding compared with VKAs in patients with eCrCL < 50 mL/min (RR, 0.83 [95% CI, 0.68-1.02]; $P = .08$). Heterogeneity was high, as evidenced by the high I^2 statistic (65%). Subgroup analysis demonstrated that apixaban and edoxaban were associated with a decreased risk for major bleeding in patients with eCrCL < 50 mL/min (apixaban—RR, 0.52 [95% CI, 0.40-0.68], $P < .000001$, $I^2 = 0\%$; edoxaban—RR, 0.77 [95% CI, 0.62-0.96], $P = .02$, $I^2 = 0\%$), whereas rivaroxaban (RR, 1.00 [95% CI, 0.79-1.26], $P = .99$, $I^2 = 22\%$) and dabigatran

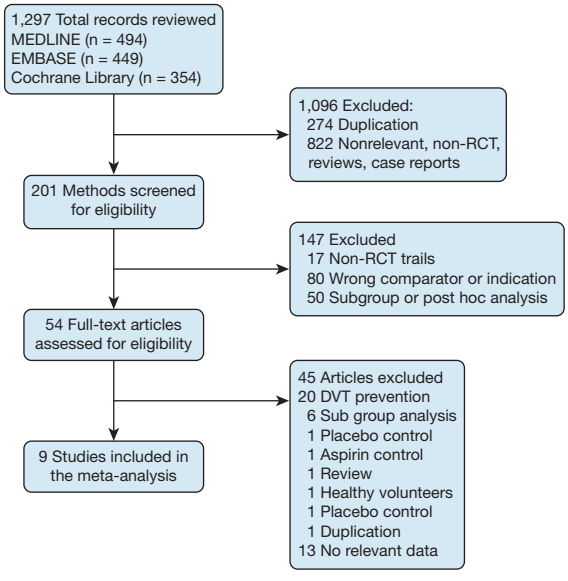


Figure 1 – *Flow chart showing systematic literature search and study selection process. RCT = randomized controlled trial.*

TABLE 1] Main Characteristics of the RCTs Included in the Meta-Analysis

Study	eCrCl-Related Exclusion Criteria	No.	Study Population	Intervention	Control	eCrCL 50 to 80 mL: DOAC group (No.)/ Control Group (No.)	eCrCL < 50 mL DOAC Group (No.)/ Control Group (No.)[a]	Follow-up, y
RE-LY,[21] 2009	eCrCl < 30 mL/min	18,113	AF	Dabigatran 150 mg bid or 110 mg BID[b]	Warfarin	5,655/2,989	2,428/1,126	2
EINSTEIN,[17] 2010	eCrCl < 30 mL/min	3,449	Acute VTE	Rivaroxaban; 15 mg bid for 3 weeks, followed by 20 mg OD	Enoxaparin followed by warfarin	390/400	120/128	0.25, 0.5, or 1
EINSTEIN-PE,[19] 2012	eCrCl < 30 mL/min	4,832	Acute PE	Rivaroxaban; 15 mg bid for 3 weeks, followed by 20 mg OD	Enoxaparin followed by warfarin	634/593	209/192	0.25, 0.5, or 1
ROCKET AF,[20] 2011	eCrCl < 30 mL/min	14,264	AF	Rivaroxaban 20 mg daily[c]	Warfarin	3,313/3,410	1,502/1,476	1.6
ARISTOTLE,[36] 2011	Cr > 221 μmol/L or eCrCl < 25 mL/ min	18,201	AF	Apixaban 5 mg bid[d]	Warfarin	3,817/3,770	1,502/1,515	1.8
J-ROCKET AF,[23] 2012	eCrCl < 30 mL/min	1,280	AF	Rivaroxaban 15 mg daily[e]	Warfarin	498/496[f]	141/143	2.5
ENGAGE AF,[16] 2013	eCrCl < 30 mL/min	21,105	AF	Edoxaban 30 or 60 mg OD[g]	Warfarin	2,985/3,030	1,287/1,348	2.8
Hokusai-VTE,[18] 2013	eCrCl < 30 mL/min	8,240	Acute VTE	Edoxaban 60 daily[g]	Warfarin	3,850/3,859[f]	268/273	1
AMPLIFY,[15] 2013	Cr > 221 μmol/ L or eCrCl < 25 mL/ min	5,395	Acute VTE	Apixaban 10 mg bid followed by 5 mg BID	Enoxaparin followed by warfarin	549/544	175/163	0.5

AF = atrial fibrillation; AMPLIFY = Apixaban for the Initial Management of Therapy; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; Cr = creatinine; DOAC = direct oral anticoagulants; eCrCl = estimated creatinine clearance; ENGAGE AF = Effective Anticoagulation With Factor Xa in Next Generation Treatment of Atrial Fibrillation; J-ROCKET AF = Japanese Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation OD = once daily; PE = pulmonary embolism; RCT = randomized controlled trial; 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.

[a]Analyses included a small number of patients with severe renal failure.

[b]Patients were randomly assigned to receive either 110-mg or 150-mg doses of dabigatran.

[c]A 15-mg dose of rivaroxaban was used in patients with eCrCl 30 to 49 mL/min.

[d]A dose of apixaban 2.5 mg bid was used in patients with ≥ 2 of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or a Cr level ≥ 1.5 mg/dL (133 μmol/L).

[e]Patients with eCrCL 30 to 49 mL/min at randomization received oral rivaroxaban 10 mg OD.

[f]eCrCL > 50 mL/min.

[g]Patients were randomly assigned to receive 60- or 30-mg doses of edoxaban. For patients in either group, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: eCrCl 30 to 50 mL/min, weight ≤ 60 kg, or the concomitant use of verapamil or quinidine.

(RR, 1.00 [95% CI, 0.81-1.24], $P = .97$) were not (e-Fig 1B).

The probability that specific DOACs may differ in their risk for major bleeding was assessed by using indirect comparisons through Bayesian network models. In patients with eCrCL 50 to 80 mL/min, no significant differences in the risk for major bleeding were observed among the different DOACs (Fig 2A). However, in patients with eCrCL < 50 mL/min, apixaban was associated with a decreased risk for major bleeding compared with other DOACs (Fig 2B).

Hemorrhagic Stroke

DOACs were associated with a decreased risk for hemorrhagic stroke compared with VKA treatment in patients with eCrCL 50 to 80 mL/min (RR, 0.43 [95% CI, 0.33-0.56]; $P < .00001$; $I^2 = 0\%$) and in patients with eCrCL < 50 mL/min (RR, 0.42 [95% CI, 0.30-0.61]; $P < .00001$; $I^2 = 0\%$) (Fig 3).

In subgroup analyses, DOAC treatment in patients with AF was associated with significantly lower risk for major bleeding compared with VKA therapy in patients with eCrCL 50 to 80 mL/min (RR, 0.89 [95% CI, 0.81-0.97]; $P = .007$; $I^2 = 11\%$) and nonsignificantly lower rates of major bleeding in those with eCrCL < 50 mL/min (RR, 0.86 [95% CI, 0.66-1.12]; $P = .18$; $I^2 = 86\%$). In patients with VTE, the DOACs were associated with significantly lower risk for major bleeding than VKA in patients with eCrCL 50 to 80 mL/min (RR, 0.84 [95% CI, 0.74-0.94]; $P < .004$; $I^2 = 0\%$) and nonsignificantly lower rates of major bleeding in patients with eCrCL < 50 mL/min (RR, 0.77 [95% CI, 0.57-1.03]; $P = 0.07$; $I^2 = 0\%$) (e-Figs 2A, 2B).

Sensitivity analysis regarding variation in study treatment duration was similar to the subgroup analysis according to indication. All studies with VTE were of relatively short duration (< 1 year), and all the studies with AF were of longer duration (> 1.6 years). Visual inspection of the funnel plots revealed no indication of publication bias (e-Fig 3).

Discussion

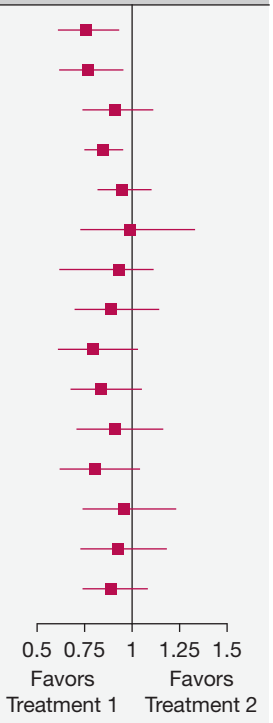
In this network meta-analysis, we found that in patients with eCrCL < 50 mL/min, apixaban is associated with lower risk for major bleeding compared with other DOACs. To our knowledge, this network meta-analysis is the largest review on the safety of DOACs in patients with RF, including nearly 94,879 patients, of whom 54,677 had RF. The nine RCTs included assessed patients receiving anticoagulant treatment for AF or VTE and reported their safety in patients with RF. Our analysis included data on 12,962 to 21,202 patients with RF who have not been included in previous meta-analyses on the safety of DOACs in patients with RF.[37-39] Our results indicate that DOACs are associated with a lower risk for hemorrhagic stroke compared with VKAs in patients with RF. Indirect comparisons by using Bayesian network meta-analysis indicated a significant credible difference among the specific DOACs in patients with eCrCL < 50 mL/min; compared with other DOACs, apixaban was associated with a significantly lower risk for major bleeding in these patients.

The associated overall risk reduction in major bleeding (especially hemorrhagic stroke) with DOACs, compared with VKAs, could have several explanations. This perceived effect might be the product of suboptimal usage of warfarin.[40] In patients treated with VKAs, increasing the time in therapeutic range (TTR) is associated with improvement in patient outcomes, including cardiovascular outcomes.[41] Post hoc analyses of some of the DOAC trials indicate that the beneficial effects of dabigatran compared with warfarin were attenuated in patients with the best international normalized ratio control.[40] The TTR of patients taking warfarin in these trials reportedly ranged between 55% and 68.4%.[10,11,14,27] Although the reported TTR in community settings are often no better,[42] no study has compared DOACs vs the gold standard of warfarin coupled with anticoagulation clinic care, in which TTRs are often > 70%.[43]

The possible disparity observed in the risk for major bleeding between apixaban and other DOACs in patients with eCrCL < 50 mL/min could be explained on the basis of the pharmacologic differences between the DOACs. They differ significantly in the degree to which their pharmacokinetics are influenced by reduced renal function. DOACs are in part excreted by the kidneys, with the highest excretion level reported with dabigatran (80%), followed by edoxaban (50%), rivaroxaban (35%), and apixaban (27 %).[10-14] Accordingly, in patients with eCrCL < 50 mL/min, the area under the plasma concentration-time curve increases 3.2- to 6.3-fold in dabigatran[44] and 1.75-, 1.52- to 1.64-, and 1.29- to 1.38-fold in edoxaban, rivaroxaban, and apixaban, respectively.[11,27,45] Based on these data, adjusted dosages were used for patients with eCrCL < 50 mL/min in some trials; however, no dose adjustment was performed for dabigatran.[21] Differences

A

Treatment 1 vs Treatment 2	OR	CrI	
Apixaban[a] vs VKA	0.76	0.61	0.93
Dabigatran 110 mg vs VKA	0.77	0.62	0.95
Dabigatran 150 mg vs VKA	0.91	0.74	1.11
Edoxaban[b] vs VKA	0.85	0.75	0.95
Rivaroxaban[c] vs VKA	0.95	0.82	1.1
Apixaban[c] vs Dabigatran 110 mg	0.99	0.73	1.33
Apixaban[c] vs Dabigatran 150 mg	0.93	0.62	1.11
Apixaban[c] vs Edoxaban[b]	0.89	0.7	1.14
Apixaban[c] vs Rivaroxaban[c]	0.8	0.61	1.03
Dabigatran 110 mg vs Dabigatran 150 mg	0.84	0.68	1.05
Dabigatran 110 mg vs Edoxaban[b]	0.91	0.71	1.16
Dabigatran 110 mg vs Rivaroxaban[c]	0.81	0.62	1.04
Dabigatran 150 mg vs Rivaroxaban[c]	0.96	0.74	1.23
Edoxaban[b] vs Dabigatran 150 mg	0.93	0.73	1.18
Edoxaban[b] vs Rivaroxaban[c]	0.89	0.74	1.08



B

Treatment 1 vs Treatment 2	OR	CrI	
Apixaban[a] vs VKA	0.49	0.37	0.65
Dabigatran 110 mg vs VKA	0.99	0.76	1.3
Dabigatran 150 mg vs VKA	1.02	0.78	1.33
Edoxaban[b] vs VKA	0.75	0.59	0.96
Rivaroxaban[c] vs VKA	0.99	0.79	1.23
Apixaban[a] vs Dabigatran 110 mg	0.5	0.34	0.74
Apixaban[a] vs Dabigatran 150 mg	0.49	0.33	0.71
Apixaban[a] vs Edoxaban[b]	0.66	0.45	0.95
Apixaban[a] vs Rivaroxaban[c]	0.5	0.35	0.72
Dabigatran 110 mg vs Dabigatran 150 mg	0.97	0.75	1.26
Dabigatran 110 mg vs Edoxaban[b]	1.31	0.92	1.89
Dabigatran 110 mg vs Rivaroxaban[c]	1	0.71	1.42
Dabigatran 150 mg vs Rivaroxaban[c]	1.03	0.73	1.47
Edoxaban[b] vs Dabigatran 150 mg	0.74	0.52	1.06
Edoxaban[b] vs Rivaroxaban[c]	0.76	0.55	1.06

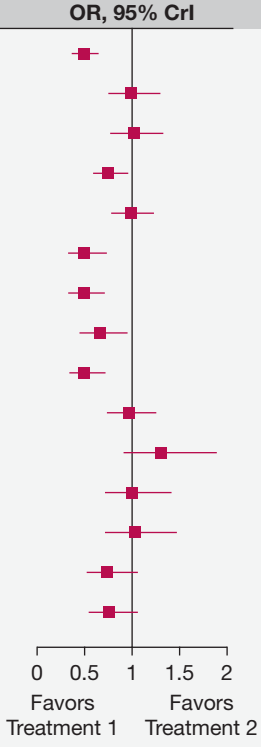


Figure 2 – *A-B, Difference between the specific medications in risk of major bleeding. A, Patients with estimated creatinine clearance (eCrCL) 50 to 80 mL/min; B, Patients with eCrCL < 50 mL/min. [a]A dose of apixaban 2.5 mg were used in patients with ≥ 2 of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or a serum creatinine level ≥ 1.5 mg/dL (133 µmol/L). [b]A dose of edoxaban 30 mg was used in patients with eCrCL < 50 mL/min or weight ≤ 60 kg. [c]A dose of rivaroxaban 15/20 mg was used in patients with eCrCL 50 to 80 mL/min; a rivaroxaban dose of 10/15 mg was used in patients with eCrCL < 50 mL/min. CrI = credible interval.*

in the risk for specific types of bleeding with DOACs compared with VKAs were also observed in the clinical trials. Significantly higher rates of GI bleeding were observed in rivaroxaban- vs VKA-treated patients[46] but not in apixaban-treated patients.[22] These pharmacokinetic differences, combined with the various dosage adjustments for each drug for patients with RF, could have led to clinically relevant differences in the relative safety of the DOACs in RF treatment.

The results of our study corroborate the main results of four previously published smaller meta-analyses on the use of DOACs in RF.[37-39,47] Compared with previous reports, our analysis included data on all four of the currently approved DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban). Moreover, we evaluated the safety outcomes for patients with eCrCL 50 to 80 mL/min and those with eCrCL < 50 mL/min. By using data from the FDA reports available at Drugs@FDA, we incorporated data that were not reported in the articles describing the safety of DOACs in patients with RF and were not included in previous meta-analyses.

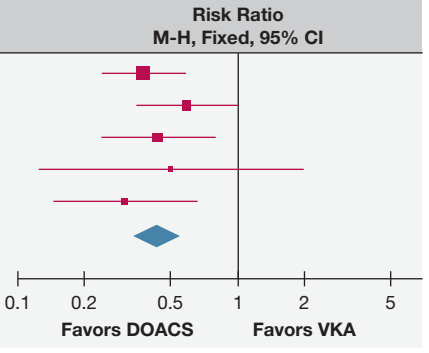
Furthermore, our analysis evaluated the relative lower risk for hemorrhagic stroke with DOACs, a rare but major complication of oral anticoagulant agents.[48] Anticoagulant-associated hemorrhagic stroke is associated with high rates of disability and death. The risk of hemorrhagic stroke is reportedly reduced by approximately 50% with the DOACs compared with standard antithrombotic treatment in the general patient population.[8] To our knowledge, for the first time, we report on a lower risk for hemorrhagic stroke in patients with eCrCL 50 to 80 mL/min or eCrCL < 50 mL/min who were treated with DOACs compared with VKA.

VKAs are currently still recommended for use in patients with end-stage renal disease.[25] However, a meta-analysis of observational studies found that the use of warfarin in these patients has an unfavorable

A

Study or Subgroup	DOACS Events	DOACS Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-LY[a] 2009	36	5,655	49	2,898	38.1%	0.38 (0.25-0.58)	2009
ROCKET AF 2011	23	5,604	39	5,617	22.9%	0.59 (0.35-0.99)	2011
ARISTOTLE 2011	16	3,817	36	3,770	21.3%	0.44 (0.24-0.79)	2011
J-ROCKET AF 2012	3	498	6	496	3.5%	0.50 (0.13-1.98)	2012
ENGAGE AF 2013	11	2,561	18	1,297	14.1%	0.31 (0.15-0.65)	2013
Total (95% CI)		**18,135**		**14,078**	**100.0%**	**0.43 (0.33-0.56)**	
Total events	89		148				

Heterogeneity: $\chi^2 = 2.64$, df = 4 ($P = .62$); $I^2 = 0\%$
Test for overall effect: $z = 6.25$ ($P < .00001$)



B

Study or Subgroup	DOACS Events	DOACS Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-LY[a] 2009	20	2,428	26	1,126	38.9%	0.36 (0.20-0.64)	2009
ROCKET AF 2011	6	1,457	11	1,456	12.0%	0.55 (0.20-1.47)	2011
ARISTOTLE 2011	7	1,502	23	1,515	25.1%	0.31 (0.13-0.71)	2011
J-ROCKET AF 2012	2	141	4	143	4.3%	0.51 (0.09-2.72)	2012
ENGAGE AF 2013	11	1,287	18	1,297	19.6%	0.62 (0.29-1.30)	2013
Total (95% CI)		**6,815**		**5,537**	**100.0%**	**0.42 (0.30-0.61)**	
Total events	46		82				

Heterogeneity: $\chi^2 = 2.16$, df = 4 ($P = .71$); $I^2 = 0\%$
Test for overall effect: $z = 4.65$ ($P < .00001$)

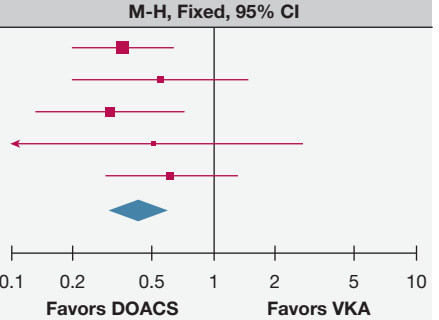


Figure 3 – *A-B, Comparison of hemorrhagic stroke risk in patients with renal failure receiving DOACs vs VKAs. Forest plot presents risk ratios for hemorrhagic stroke in DOACs compared with standard treatment in patients with (A) eCrCl 50 to 80 mL/min and (B) eCrCl < 50 mL/min. ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; DOAC = direct oral anticoagulant; ENGAGE AF = Effective Anticoagulation With Factor Xa in Next Generation Treatment of Atrial Fibrillation; J-ROCKET AF = Japanese Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation M-H = Mantel-Haenszel test; 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; VKA = vitamin K antagonist. See Figure 2 legend for expansion of other abbreviation. [a]Intracranial bleed.*

risk/benefit ratio.[49] Further studies are required to assess DOAC use in patients with severe RF.

Our study has several limitations shared by all meta-analyses. First, for some analyses, there was high heterogeneity among the included trials. To circumvent high heterogeneity in some studies, the random effects model was used, and we explored the possibility that the heterogeneity may be attributable to the safety of various DOACs by using a network meta-analysis model.[50] Second, although 22 studies met the inclusion criteria for our analysis, safety data for patients with RF were available for only nine studies. The studies that were not included in our analyses were mostly smaller and included only 11,117 patients, whereas our analysis included 94,879 patients. It is therefore unlikely that outcomes data from these studies would significantly change our conclusions. Third, our analysis aggregated subgroup post hoc analyses of DOACs in the RF population, although the trials were not specifically designed to assess the treatment effect of DOACs in patients with RF.

Conclusions

DOACs are associated with reduced risk for hemorrhagic stroke compared with VKA therapy in patients with eCrCL 50 to 80 mL/min and eCrCL $<$ 50 mL/min, and with reduced risk for major bleeding compared with VKAs in patients with eCrCL 50 to 80 mL/min. However, DOACs may differ substantially from each other in their RR for major bleeding in patients with eCrCL $<$ 50 mL/min. Clinical trials with direct comparisons between DOAC medications are necessary to confirm these findings.

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Author contributions: B. H. R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; contributed to study design, collection of data, and data analysis; and wrote the first draft of the manuscript. A. Perlman contributed to study design, collection of data, study interpretation, and writing of the manuscript. I. M. and M. M. directed the research and contributed to study design, analysis of data, interpretation of study results, and writing of the manuscript. H. D. D. and A. Pollak provided critical appraisal and revision, and contributed substantially to study interpretation and the writing of the manuscript.

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