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Research paper

Oral anticoagulants and relative risk of acute kidney injury in patients with atrial fibrillation: A systematic review and network meta-analysis

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ABSTRACT

Study objective: Oral anticoagulants (direct oral anticoagulants [DOACs] or warfarin) prevent stroke in patients with atrial fibrillation (AF), but their use may be associated with acute kidney injury (AKI). We aimed to compare AKI risk across individual oral anticoagulants in patients with AF.
Design: Systematic review and network meta-analysis.
Setting: Randomized trials and population-based studies.
Participants: Patients with AF.
Interventions: Oral anticoagulants.
Main outcome measures: AKI.
Results: A systematic literature search in Medline and Embase databases performed on December 17, 2021 identified ten randomized trials and eight population-based longitudinal studies based on prespecified inclusion criteria for systematic review. Clinical trials had short follow-ups and reported only low event rates of serious AKI. Retrospective longitudinal studies were assessed to be at higher risk for bias from confounding and outcome ascertainment, but follow-up was longer (1.5 to 8 years), with AKI incidence ranging from 2 to 29/100 person-years. Eight longitudinal studies that met transitivity assumption were included in a random-effects network meta-analysis within a Bayesian framework. All DOACs were associated with significantly lower risk of AKI compared to warfarin. Dabigatran was associated with lower risk of AKI compared to apixaban (hazard ratio [HR] = 0.82; 95% confidence interval [CI]: 0.68–0.99), rivaroxaban (HR = 0.84; 95%CI: 0.72–0.98), and warfarin (HR = 0.68; 95%CI: 0.59–0.77). Effect size estimates varied by chronic kidney disease status and study geographic locations.
Conclusion: Apixaban, rivaroxaban, and dabigatran were associated with lower long-term risk of AKI compared to warfarin among patients with AF, with dabigatran potentially associated with the lowest risk.

1. Introduction

Atrial fibrillation is the most prevalent cardiac arrhythmia, affecting approximately 33 million persons worldwide [1]. Patients with atrial fibrillation are often treated with oral anticoagulants to prevent systemic thromboembolism and stroke. More than two million patients with atrial fibrillation receive oral anticoagulation therapy [2]. Common oral anticoagulants include warfarin and direct oral anticoagulants (DOACs), i.e., apixaban, rivaroxaban, edoxaban, and dabigatran. DOACs have been increasingly prescribed because of their effectiveness, fewer therapeutic drug monitoring requirements, and lower bleeding risk compared to warfarin.

Currently, individual DOACs are considered equivalent in efficacy and safety in most clinical settings [3,4]. All oral anticoagulants, including warfarin and DOACs, have the potential to cause acute kidney injury (AKI). Several mechanisms including glomerular hemorrhage, IgA nephropathy, and acute interstitial nephritis have been proposed [2,5–7]. AKI can lead to significant short- and long-term morbidities such as uremia and end-stage kidney disease, particularly in the setting of cardiovascular comorbidities and chronic kidney disease (CKD),

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which frequently coexist in patients with atrial fibrillation. Clinical trials, however, have not assessed serious AKI as a major safety outcome [8–17]. In population-based observational studies, a substantive incidence of AKI among users of oral anticoagulants has been observed [18–25]. While DOACs were often associated with a lower risk of AKI compared to warfarin, the incidence of AKI and relative risks have varied across study populations and patient subgroups [18–25]. Few studies have directly compared AKI risks across individual DOACs.

The objective of this study was to conduct a systematic review, which provides a platform for comparisons of study characteristics, incidence, and relative risks of AKI across clinical trials and post-marketing, population-based studies, and use network meta-analysis to investigate whether an individual DOAC was associated with lower risk of AKI compared to the others.

2. Materials and methods

This study was registered at PROSPERO (CRD42021292725) where the study protocol can be accessed. We present this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Supplemental appendix 1).

2.1. Search strategy and inclusion criteria for systematic review

Two reviewers worked independently to systematically search Medline and Embase databases for study records published on or before December 17, 2021 using a combination of the following terms including their acronyms: atrial fibrillation, direct oral anticoagulants, apixaban, rivaroxaban, edoxaban, dabigatran, and warfarin (Supplemental appendix 2). We applied study design filters for clinical trials or observational studies. We screened titles and abstracts of potentially relevant records and reviewed full-length articles to identify studies eligible for systematic review using the following inclusion criteria: (1) randomized clinical trial or longitudinal study, (2) study population of patients with atrial fibrillation, (3) AKI (described below) at any time point after initiation of oral anticoagulation therapy reported as either a prespecified study outcome or an adverse medication event, and (4) comparison of outcomes between at least two oral anticoagulants including apixaban, dabigatran, rivaroxaban, edoxaban, or warfarin.

2.2. Data extraction and risk of bias assessment

Two reviewers independently extracted data from each study included for systematic review according to PRISMA guidelines. We summarized study characteristics including publication year, language, journal, study population, sample size, comparator oral anticoagulants, study design, statistical method, AKI ascertainment, follow-up period, the incidence of AKI, and subgroup analysis. For clinical trials, we obtained any additional AKI-related data from clinicaltrials.gov. We assessed risks of bias based on the potential for confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, selection of reported result – domains adapted from the Newcastle-Ottawa Scale (NOS) system [26]. Conflicts in assessments between reviewers were resolved via discussion among all authors.

2.3. Outcome definition

AKI was assessed as either a primary study endpoint or an adverse medication event reported by the authors of the original studies. Studies that did not prespecify definition of AKI based on the change in serum creatinine levels or administrative codes such as International Classification of Diseases (ICD) codes were not included.

2.4. Assessment of transitivity

We reviewed each study's population characteristics, study design, and analytical methods to assess transitivity and potential for inclusion in meta-analysis.

2.5. Statistical analysis

In a meta-analysis, we first combined direct treatment comparison results from individual studies using random-effects models, assuming a distribution of true effects. Inter-study heterogeneity was evaluated using the I^2 statistic. We then constructed random-effects networks within a Bayesian framework using the Markov chain Monte Carlo methods and performed network meta-analysis with a consistency model to simultaneously compare all oral anticoagulants. Testing for inconsistency was not indicated when there was only one single common comparator across studies [27]. We generated cumulative ranking curves for all treatments and ranked them based on the surface under the cumulative ranking curve (SUCRA). We conducted a subgroup analysis in patients with CKD, which was defined as either a documented past medical history of CKD or estimated glomerular filtration rate (eGFR) of 30–60 ml/min/1.73m^2 (based on either medical records or lab measurements of creatinine levels) upon initiation of oral anticoagulant for atrial fibrillation. We did not include patients with eGFR of 30 ml/min/1.73m^2 or below because DOACs are generally avoided in these patients according to clinical guidelines. We conducted sensitivity analyses excluding studies that overlapped in data sources, not published in peer-reviewed journals, or based on the geographic locations of study populations. Publication bias was not assessed if fewer than ten studies were involved in meta-analysis. A two-sided p-value of 0.05 was used as the cutoff for statistical significance. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX) and the “gmetc” and “rjags” packages in R (R Foundation, Version 3.3.3).

3. Results

3.1. Literature search

We identified 9820 items via literature search of Medline and Embase databases on December 17, 2021 of which 8780 titles and abstracts were screened. After reviewing 219 full-length articles, we identified ten clinical trials and eight longitudinal observational studies for systematic review and assessment of eligibility for meta-analysis (Fig. 1 and Table 1) [8–25]. All studies were published in English.

3.2. Study characteristics

All ten clinical trials were randomized, controlled, and multi-center. Nine were multinational. Four trials involved direct comparisons between rivaroxaban and warfarin, two involved direct comparisons between apixaban and warfarin, two involved direct comparisons between dabigatran and warfarin, and two involved direct comparisons between edoxaban and warfarin (Fig. 2a). AKI was not described in the main texts of published articles but reported in clinicaltrials.gov as adverse events only when serious (i.e., life-threatening, requiring inpatient hospitalization or extending a hospital stay, or resulting in significant incapacity). Five studies had a follow-up time of less than one year. Only cumulative incidence by treatment arm but not time-to-event data or measures of association was reported.

In addition to clinical trials, we identified eight real-world (post-marketing, population-based), longitudinal studies evaluating AKI risk among long-term oral anticoagulant users. Seven studies were published in peer-reviewed journals. One was published as a conference abstract [25]. Two pairs of studies utilized partially overlapping data [18,20,22,23]. The combined study population consisted of those with and without CKD from four countries across three continents (Asia,

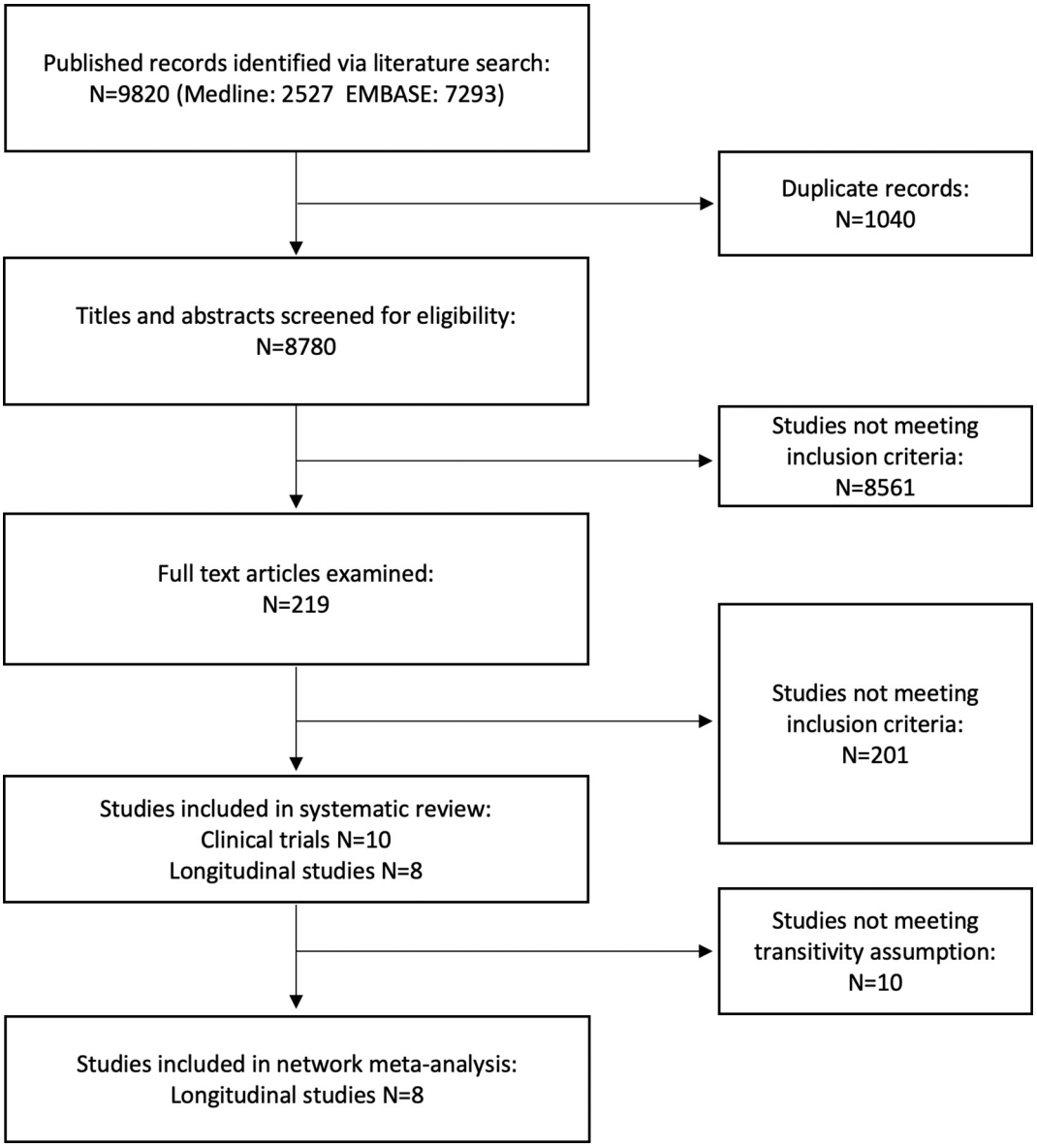

Fig. 1. Study selection.

Europe, and North America). All but one study constructed cohorts using inverse probabilities of treatment weighting on derived propensity scores [25]. Cox proportional hazards regression was used to assess risks of AKI in all studies. None included edoxaban as a treatment comparator, and warfarin was the only common comparator (Fig. 2b and c). There was no head-to-head comparison between DOACs. Measures of association were hazard ratios (HRs) with 95% confidence intervals (CIs) in all studies. In two studies, AKI was ascertained based on creatinine lab values [24,25]. In other studies, the outcome was ascertained using ICD codes. The follow-up periods ranged from 1.5 to 8 years. The incidence of AKI ranged from 2 to 29 per 100 person-years. Seven studies performed subgroup analysis by either history of CKD or strata of eGFR, two of which studied the subgroup of patients with eGFR of 30 ml/min/1.73m^2 or below. One study did not report subgroup analysis results.

3.3. Risk of bias and transitivity assessment

In the assessment of risk for bias and transitivity, confounding and outcome ascertainment were considered potential sources of bias across retrospective studies (Supplemental Table 1). Transitivity assumption was considered met among eight retrospective studies but violated among clinical trials (different study populations and highly variable follow-up periods without available time-to-event data) (Supplemental Table 2). Therefore, only those eight retrospective longitudinal studies were included in the subsequent meta-analysis.

3.4. Meta-analysis of direct treatment comparisons and evaluation of heterogeneity

We combined effect estimates from direct comparisons of AKI risk between treatments in a meta-analysis. Compared to warfarin, each DOAC was associated with a significantly lower risk of AKI (HR = 0.82, 95%CI: 0.74–0.91 for apixaban; HR = 0.81, 95%CI: 0.76–0.86 for rivaroxaban; HR = 0.68, 95%CI: 0.59–0.77 for dabigatran; Fig. 3a). There was minimal heterogeneity across studies in this meta-analysis (I^2 = 0, p = 0.90 for apixaban vs warfarin; I^2 = 17.2%, p = 0.30 for rivaroxaban vs warfarin; I^2 = 0, p = 0.89 for dabigatran vs warfarin). The risk of AKI remained significantly lower comparing each DOAC to warfarin in patients without or with CKD, defined by either documented

Table 1
Characteristics of studies selected for systematic review.

First author and year of publication	Study population	Oral anticoagulants	Study design/analytical approach to acute kidney injury risk	Definition of acute kidney injury and follow-up period	Incidence or cumulative incidence of acute kidney injury	Subgroup analyses
Randomized clinical trials						
Ezekowitz et al., 2018 [8]	Patients with recent diagnosis of atrial fibrillation scheduled for cardioversion from 12 countries	Apixaban (5 mg twice daily or 2.5 mg twice daily if age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 133 μmol/l) vs warfarin	Randomized, active-controlled, open-label trial; cumulative incidence	Acute kidney injury as a serious adverse event[a] in the 30 days following cardioversion	1/735 (apixaban) vs 5/721 (warfarin)	NA
Calkins et al., 2017 [9]	Patients with paroxysmal or persistent nonvalvular atrial fibrillation with planned ablation from 11 countries	Dabigatran (150 mg twice daily) or warfarin, uninterrupted pre- and post-catheter ablation	Randomized, open-label, controlled trial; cumulative incidence	Acute kidney injury as a serious adverse event between 4 and 8 weeks pre-ablation and 8 weeks post-ablation	1/338 (dabigatran) vs 1/338 (warfarin)	NA
Goette et al., 2016 [10]	Patients with atrial fibrillation no shorter than 48 h and no longer than 12 months and who underwent electrical cardioversion from 19 countries	Edoxaban 60 mg daily (or 30 mg daily if creatinine clearance 15–50 ml/min, weight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors) vs warfarin	Randomized, open-label trial; cumulative incidence	Acute kidney injury as a serious adverse event between 21 days prior to procedure and 28 days afterwards	3/1067 (edoxaban) vs 2/1082 (warfarin)	NA
Gibson et al., 2016 [11]	Patients with atrial fibrillation who underwent percutaneous coronary intervention with stent placement from 25 countries	Rivaroxaban 15 mg daily plus a P2Y12 inhibitor vs rivaroxaban 2.5 mg twice daily plus DAPT vs warfarin plus DAPT	Randomized, open-label trial; cumulative incidence	Acute kidney injury as a serious adverse event in 12 months	2/696 (rivaroxaban plus plus a P2Y inhibitor) vs 2/706 (rivaroxaban plus DAPT) vs 1/697 (warfarin plus DAPT)	NA
Cappato et al., 2014 [12]	Patients with atrial fibrillation undergoing cardioversion from 16 countries	Rivaroxaban 20 mg daily (or 15 mg daily if creatinine clearance was between 30 and 49 ml/min) vs warfarin	Randomized, open-label, parallel-group trial; cumulative incidence	Acute kidney injury as a serious adverse event between one day to 8 weeks prior to cardioversion and 6 weeks afterwards	0/988 (rivaroxaban) vs 2/499 (warfarin)	NA
Giugliano et al., 2013 [13]	Patients with moderate-to-high-risk atrial fibrillation from 46 countries	Edoxaban 60 mg daily vs 30 mg daily vs warfarin (edoxaban doses were halved if creatinine clearance 30–50 ml/min, weight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors)	Three-group, randomized, double-blind, double-dummy trial; cumulative incidence	Acute kidney injury as a serious adverse event in 3.5 years	53/7012 (edoxaban 60 mg daily) vs 62/7002 (edoxaban 30 mg daily) vs 63/7012 (warfarin)	NA
Hori et al., 2012 [14]	Japanese patients with atrial fibrillation at elevated risk for stroke	Rivaroxaban (15 mg daily or 10 mg daily if creatinine clearance 30–49 ml/min) or warfarin	Randomized, double-blind, double-dummy, parallel-group, active-controlled trial; cumulative incidence	Acute kidney injury as a serious adverse event between June 8, 2007 and January 19, 2010	1/639 (rivaroxaban) vs 0/639 (warfarin)	NA
Patel et al., 2011 [15]	Patients with atrial fibrillation at moderate-to-high risk for stroke from 45 countries	Rivaroxaban 20 mg daily (or 15 mg daily if creatinine clearance 30–49 ml/min) vs warfarin	Randomized, double-blind trial; cumulative incidence	Acute kidney injury as a serious adverse event between December 18, 2006 and May 28, 2010	37/7111 (rivaroxaban) vs 46/7125 (warfarin)	NA
Granger et al., 2011 [16]	Patients with atrial fibrillation with one or more risk factors for stroke from 39 countries	Apixaban 5 mg twice daily (or 2.5 mg twice daily if age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 133 μmol/l) vs warfarin	Randomized, double-blind trial; cumulative incidence	Acute kidney injury as a serious adverse event between December 19, 2006 and April 2, 2010	35/9052 (apixaban) vs 57/9088 (warfarin)	NA
Connolly et al., 2009 [17]	Patients with atrial fibrillation from 44 countries	Dabigatran 110 mg twice daily vs dabigatran 150 mg twice daily vs warfarin	Randomized, noninferiority trial; cumulative incidence	Acute kidney injury as a serious adverse event between December 22, 2005 and March 15, 2009	38/6059 (dabigatran 150 mg twice daily) vs 42/5983 (dabigatran 110 mg twice daily) vs 35/5998 (warfarin)	NA
Longitudinal studies						
Harel et al., 2021 [24][b]	Patients ≥66 years old with atrial fibrillation (ICD-10 = I48) in the Canadian Institute for Health Information's Discharge Abstract Database and the Ontario	Apixaban (N = 8217) vs warfarin (N = 8383); rivaroxaban (N = 5263) vs warfarin (N = 5363); dabigatran (N = 2277) vs warfarin (N = 2269)	Population-based retrospective cohort constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	KDIGO Work Group laboratory criteria comparing creatinine levels during a hospitalization or emergency room visit to those at the most recent outpatient	11.1 (apixaban) vs 14.2 (warfarin); 9.1 (rivaroxaban) vs 11.1 (warfarin); 6.4 (dabigatran) vs 10.2	EGFR by CKD-EPI Equation (>60, 30–60, and <30 ml/min/1.73m^2), time of INR in therapeutic range

(*continued on next page*)

Table 1 (*continued*)

First author and year of publication	Study population	Oral anticoagulants	Study design/analytical approach to acute kidney injury risk	Definition of acute kidney injury and follow-up period	Incidence or cumulative incidence of acute kidney injury	Subgroup analyses
	Laboratories Information System in Ontario Canada			visit in the preceding 365 days between January 2009 and March 2017	(warfarin) per 100 person-years	
Perez et al., 2021 [25][b]	Patients with non-valvular atrial fibrillation identified using primary care electronic health records in the United Kingdom	Rivaroxaban 15/20 mg daily (N = 6746) vs warfarin (N = 7457)	Retrospective cohort study; Cox proportional hazards regression	Aberdeen acute kidney injury phenotyping algorithm based on all recorded renal function laboratory values between January 2014 and March 2019	1.9 (rivaroxaban) vs 2.4 (warfarin) per 100 person-years	History of CKD
Hernandez et al., 2020 [23][b]	Patients with history of diabetes mellitus and atrial fibrillation (ICD-10 = I48) without codes for valvular disease in the IBM MarketScan database in the United States	Rivaroxaban (N = 10,017) vs warfarin (N = 11,665)	Population-based retrospective cohort constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	ICD10 = N-17 during an emergency department visit or hospital admission between January 2011 and December 2017	7.7 (rivaroxaban) vs 13.5 (warfarin) per 100 person-years	Age (≥70 and <70 years), sex, history of CKD, history of hypertension
Coleman et al., 2019 [22][b]	Patients with ≥2 inpatient or outpatient ICD codes for atrial fibrillation and without codes suggesting valvular disease in the Truven MarketScan database in the United States	Rivaroxaban (N = 36,318) vs warfarin (N = 36,281)	Population-based retrospective cohort constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	ICD10 = N-17 during an emergency department visit or hospital admission between January 2012 and December 2017	4.9 (rivaroxaban) vs 8.5 (warfarin) per 100 person-years	Age (≥70 and <70 years), history of ACE-I/ARB use, and CHA2DS2-VASc score (0–1, 2–3, and >4)
Shin et al., 2018 [21][b]	Patients with atrial fibrillation (ICD9-CM code 427.x) in a community-based large, tertiary health system between October 2010 and February 2017 in the United States	Apixaban (N = 1029) vs warfarin (N = 1029); rivaroxaban (N = 1325) vs warfarin (N = 1325); dabigatran (N = 852) vs warfarin (N = 852)	Population-based retrospective cohort constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	ICD-9-CM codes 584.x between October 2010 and February 2017	9.5 (overall study population) per 100 person-years	EGFR by CKD-EPI Equation (>60, 30–60, and <30 ml/min/ 1.73m^2)
Chan et al., 2018 [20][b]	Patients with atrial fibrillation (ICD-9-CM = 427, ICD-10 = I48) in the National Health Insurance Program in Taiwan	Apixaban (without CKD, N = 4368; with CKD, N = 1507) vs warfarin (without CKD, N = 16,908; with CKD, N = 4227); rivaroxaban (without CKD, N = 22,301; with CKD, N = 5765) vs warfarin (without CKD, N = 16,908; with CKD, N = 4227); dabigatran (without CKD, N = 16,945; with CKD, N = 3200) vs warfarin (without CKD, N = 16,908; with CKD, N = 4227)	Population-based retrospective cohorts (with or without CKD) constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	ICD-9- CM 580.X, 584.X, or 586 (until January 1, 2016) and ICD-10-CM N17.x (from January 1, 2016 to December 31, 2016) during hospitalization or an outpatient visit between June 2012 and December 2016	Without CKD: 5.0 (apixaban) vs 4.7 (rivaroxaban) vs 2.2 (dabigatran) vs 6.0 (warfarin) per 100 person-years With CKD: 20.7 (apixaban) vs 16.7 (rivaroxaban) vs 14.9 (dabigatran) vs 28.7 (warfarin) per 100 person-years	History of CKD (ICD-9-CM 580–589)
Yao et al., 2017 [19][b]	Patients with atrial fibrillation identified using OptumLabs (Cambridge, Massachusetts) Data Warehouse which contains privately insured and Medicare Advantage enrollees in the United States	Apixaban (N = 1883) vs warfarin (N = 4185); rivaroxaban (N = 2485) vs warfarin (N = 4185); dabigatran (N = 1216) vs warfarin (N = 4185)	Population-based retrospective cohort constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	Diagnosis code at the primary or secondary position during a hospitalization or emergency department visit between October 2010 and April 2016	9.9 (apixaban) vs 6.9 (rivaroxaban) vs 4.9 (dabigatran) vs 12.6 (warfarin) per 100 person-years	EGFR by CKD-EPI Equation (≥60 and <60 ml/min/1.73m^2), mean INR in warfarin-treated patients
Chan et al., 2016 [18][b]	Patients with newly diagnosed atrial fibrillation (ICD-9-CM code 427.31) in the Taiwan National Health Insurance Registry Database	Dabigatran (without CKD, N = 7702; with CKD, N = 2256) vs warfarin (without CKD, N = 7885; with CKD, N = 2089)	Population-based retrospective cohorts (with or without CKD) constructed using inverse probabilities of treatment weighting based on propensity scores; Cox proportional hazards regression	ICD-9-CM 580.X, 584.X, or 586 during hospitalization or an outpatient visit between June 2012 and December 2013	Without CKD: 2.2 (dabigatran) vs 3.5 (warfarin) per 100 person-years With CKD: 9.3 (dabigatran) vs 16.2 (warfarin) per 100 person-years	History of CKD (ICD-9-CM 580–589)

ACE-I/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. CKD, chronic kidney disease. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration. DAPT, dual antiplatelet therapy. EGFR, estimated glomerular filtration rate. ICD-9-CM, International Classification of Diseases-9-Clinical Modification code. ICD-10, International Classification of Diseases 10th Revision. INR, iinternational normalized ratio. KDIGO, Kidney Disease: Improving Global Outcomes. NA, not available.

[a] Serious adverse event was defined as one that resulted in death, was life-threatening, required inpatient hospitalization or extended a current hospital stay, resulted in an ongoing or significant incapacity or interfered substantially with normal life functions, caused a congenital anomaly or birth defect, or required medical or surgical intervention to prevent any of these outcomes.

[b] Studies meeting transitivity assumption and subsequently included in a network meta-analysis.

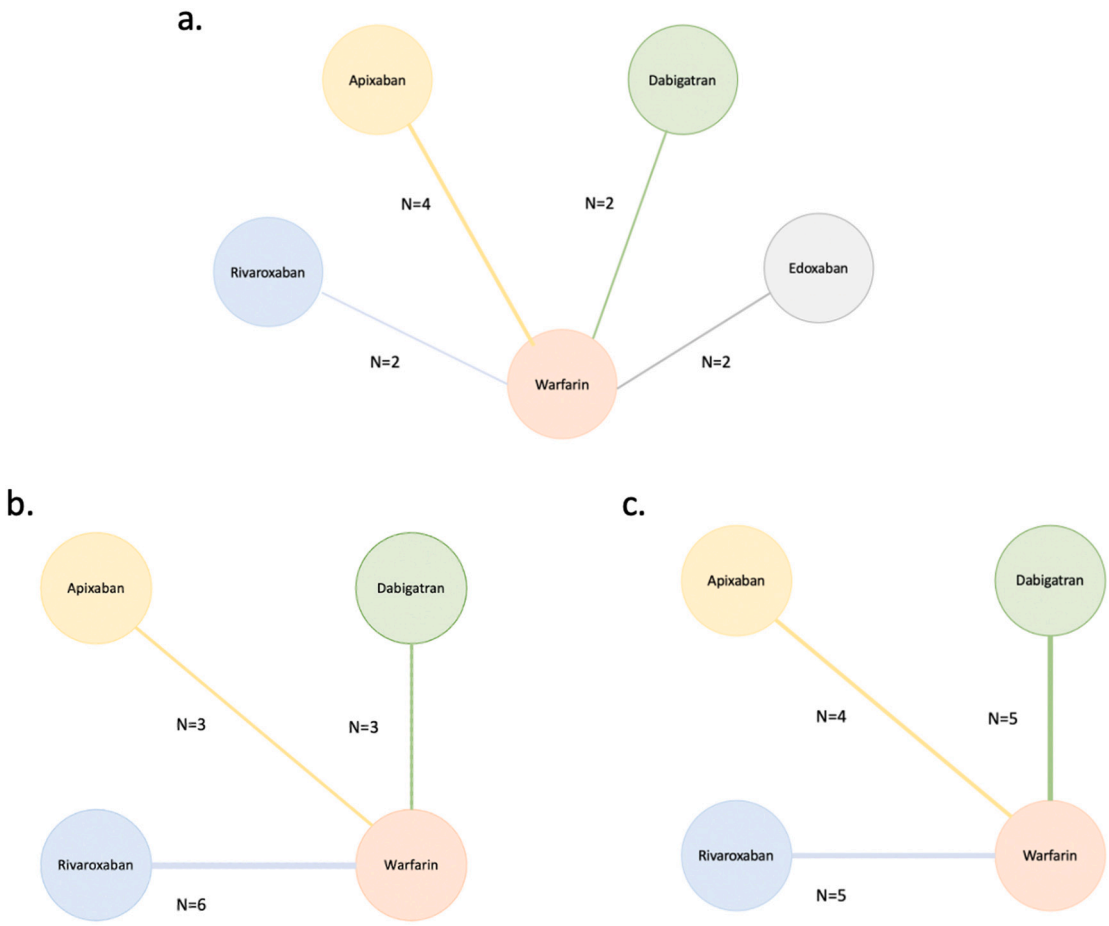

Fig. 2. Summary of direct treatment comparisons in randomized trials (a), longitudinal studies overall (b) and in studies stratifying patients by documented history of chronic kidney disease or strata of estimated glomerular filtration rate (c).

history or eGFR (Fig. 3b and c). In patients with a documented history of CKD or eGFR of 30–60 ml/min/1.73m^2, effect sizes were larger comparing each DOAC to warfarin. Compared to the main analysis, high degrees of inter-study heterogeneity were observed for apixaban and rivaroxaban, but not dabigatran.

3.5. *Network meta-analysis and ranking of treatments*

In network meta-analysis, there was no difference in risk of AKI comparing apixaban to rivaroxaban (HR = 1.02, 95%CI 0.89–1.17; Table 2). Dabigatran was associated with statistically significant 18% and 16% lower risks of AKI than apixaban (HR = 0.82, 95% CI: 0.68–0.99) and rivaroxaban (HR = 0.84, 95% CI: 0.72–0.98). The probability of being ranked first for the lowest AKI risk was 2%, 1%, 97%, and <0.01% for apixaban, rivaroxaban, dabigatran, and warfarin respectively (Fig. 4). SUCRA was 0.46, 0.55, 0.99, and 0.001 for apixaban, rivaroxaban, dabigatran, and warfarin respectively. In patients with a documented history of CKD or eGFR of 30–60 ml/min/1.73m^2, directions of associations remained similar. Still, there were variations in effect size estimates and wider confidence intervals for analyses of apixaban and rivaroxaban but not dabigatran.

3.6. *Sensitivity analyses*

In sensitivity analysis, findings were consistent after excluding studies overlapping in data sources or those not published in peer-reviewed journals (Supplemental Tables 3 and 4). Consistency in effect size estimates improved, and heterogeneity was lower across subgroup analyses by CKD status or eGFR of 30–60 ml/min/1.73m^2 for apixaban and rivaroxaban when including only populations from European and North American regions (Supplemental Table 5 and Supplemental Figure).

4. Discussion

In this systematic review and meta-analysis, we summarized data on AKI from clinical trials and population-based retrospective studies in broad populations of individuals with AF and with and without mild-to-moderate CKD. Through network meta-analysis of longitudinal studies, we confirmed that apixaban, rivaroxaban, and dabigatran each individually associated with a lower risk of AKI then warfarin. Compared to other DOACs, dabigatran was associated with the lowest risk of AKI, a finding that may be attributable to pharmacologic properties of the medication, geolocation differences, or confounding.

Oral anticoagulants are widely prescribed in patients with AF, with DOACs now supported by a class I recommendation over warfarin in eligible patients [4]. Benefits of DOACs include a favorable safety profile, fewer therapeutic drug monitoring requirements and dietary restrictions, and non-inferior efficacy in preventing thromboembolism and stroke. All oral anticoagulants can theoretically cause AKI via glomerular hemorrhage [2]. In clinical trials of DOACs in atrial fibrillation, the number of severe AKI events was low [13,15–17]. In these studies, AKI was not assessed as a safety endpoint, the follow-up periods were short, and ascertainment and detailed classification of AKI events including time-to-event data were lacking.

In contrast, real-world studies with longer follow-up reported sizeable AKI incidence among oral anticoagulant users. Through inverse probability of treatment weighting and time-to-event analysis, a lower

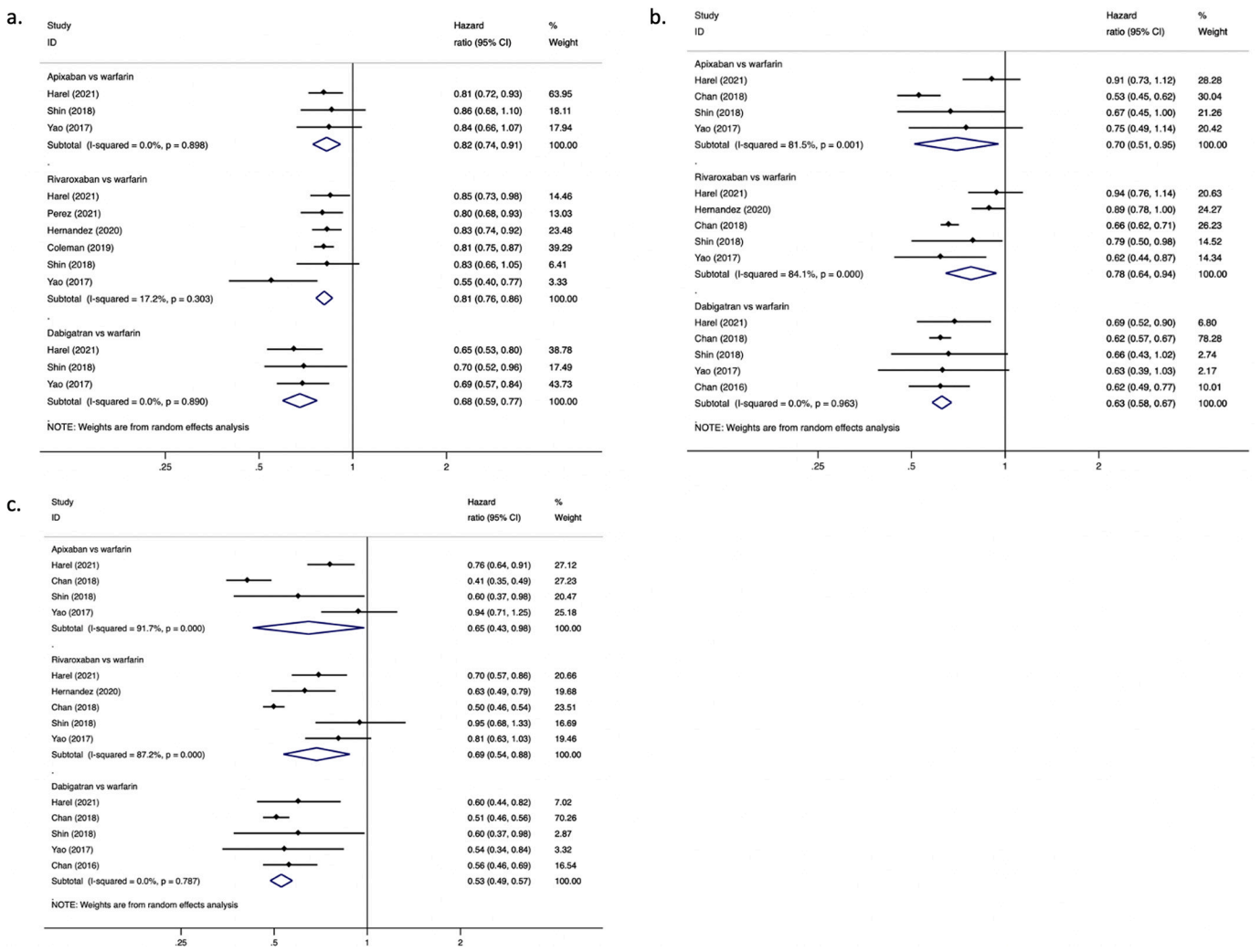

Fig. 3. Combined effect estimates from individual direct comparisons of acute kidney injury risk between oral anticoagulants overall (a), in patients with no documented history of chronic kidney disease or estimated glomerular filtration rate > 60 ml/min/1.73m^2 (b), and in patients with a documented history of chronic kidney disease or estimated glomerular filtration rate of 30–60 ml/min/1.73m^2 (c).

AKI risk has been associated with DOACs than warfarin in most of these studies. Such difference in risk may be attributable to higher glomerular bleeding risk in warfarin users due to challenges in maintaining therapeutic drug levels. One subgroup analysis including only warfarin users with high percentages of therapeutic-range international normalized ratio found similar AKI risk compared to that in DOACs users [24]. It is also possible that AKI results from the prothrombotic milieu of atrial fibrillation itself, and DOACs provide greater protection against this complication compared to warfarin. Alternative mechanisms underlying AKI in oral anticoagulant users may exist – there have been case reports of biopsy-proven acute interstitial nephritis and IgA nephropathy in these patients [5–7].

Two systematic reviews and meta-analyses have compared renal outcomes between DOAC and warfarin users [28,29]. These studies evaluated DOACs as a single class of medication without differentiating between individual agents. Randomized clinical trials and cohort studies were included in the same analysis despite differences in study designs and populations, resulting in high heterogeneity. In comparison, our systematic review and meta-analysis separately evaluated clinical trials and longitudinal studies. We included a large sample of patients from the greatest number of real-world studies. Importantly, we used network meta-analysis as an approach to simultaneous comparisons across individual DOACs, which highlighted the possibility of dabigatran being associated with the lowest risk of AKI among oral anticoagulants, a finding that has not been described in the literature to date. This may be explained by the unique pharmacological properties of dabigatran as a direct thrombin inhibitor as opposed to other DOACs which are factor Xa inhibitors. We note that the clearance of dabigatran is more dependent on renal function (renal clearance>80%) compared to apixaban (renal clearance~27%) and rivaroxaban (renal clearance~36%) [30]. Because of a lower renal clearance, apixaban may be favored over other DOACs in patients with lower kidney function when warfarin was not a feasible option – a Class IIB recommendation per most recent guidelines [4,30,31]. Although those with eGFR<30 ml/min/1.73m^2 were not included in our subgroup analysis of patients with CKD, we did find larger effect sizes for dabigatran vs other oral anticoagulants in patients with CKD compared to those without, which may indicate residual confounding-by-indication. Interestingly, in subgroup analysis by geographic regions, we observed lower heterogeneity and highly consistent effect sizes regardless of CKD status, where dabigatran remained the agent associated with the lowest AKI risk, implying possible contribution of geolocation differences in study populations and clinical practice to heterogeneity in the main network meta-analysis.

Patients with advanced CKD are subject to substantially higher bleeding risks because of unpredictable renal function fluctuations and uremic platelet dysfunction, making anticoagulation therapy challenging [32]. Unfortunately, there is a paucity of data on the efficacy

Table 2
Hazard ratios and 95% confidence intervals for acute kidney injury associated with apixaban, rivaroxaban, dabigatran, and warfarin from network meta-analysis.

	Apixaban	Rivaroxaban	Dabigatran	Warfarin
Overall[a]				
Compared to apixaban	1	0.98 (0.85, 1.12)	0.82 (0.68, 0.99)	1.22 (1.10, 1.35)
Compared to rivaroxaban	1.02 (0.89, 1.17)	1	0.84 (0.72, 0.98)	1.23 (1.16, 1.32)
Compared to dabigatran	1.22 (1.01, 1.46)	1.19 (1.02, 1.39)	1	1.47 (1.30, 1.69)
Compared to warfarin	0.82 (0.74, 0.91)	0.81 (0.76, 0.86)	0.68 (0.59, 0.77)	1
Patients without CKD[b,c]				
Compared to apixaban	1	1.12 (0.83, 1.50)	0.93 (0.69, 1.24)	1.43 (1.05, 1.96)
Compared to rivaroxaban	0.89 (0.67, 1.20)	1	0.82 (0.63, 1.08)	1.28 (1.06, 1.56)
Compared to dabigatran	1.08 (0.81, 1.46)	1.21 (0.92, 1.59)	1	1.59 (1.49, 1.72)
Compared to warfarin	0.70 (0.51, 0.95)	0.78 (0.64, 0.94)	0.63 (0.58, 0.67)	1
Patients with CKD				
Compared to apixaban	1	1.02 (0.65, 1.57)	0.80 (0.50, 1.24)	1.54 (1.02, 2.33)
Compared to rivaroxaban	0.98 (0.64, 1.53)	1	0.78 (0.51, 1.19)	1.45 (1.14, 1.85)
Compared to dabigatran	1.25 (0.81, 1.99)	1.28 (0.84, 1.95)	1	1.89 (1.75, 2.04)
Compared to warfarin	0.65 (0.43, 0.98)	0.69 (0.54, 0.88)	0.53 (0.49, 0.57)	1

[a] Studies included: Harel et al., 2021, Perez et al., 2021, Hernandez et al., 2020, Coleman et al., 2019, Shin et al., 2018, Yao et al., 2017.
[b] Studies included: Harel et al., 2021, Hernandez et al., 2020, Chan et al., 2018, Shin et al., 2018, Yao et al., 2017, Chan et al., 2016.
[c] CKD, chronic kidney disease, defined as either a documented history of chronic kidney disease or estimated glomerular filtration rate of 60 ml/min/1.73m^2 or less.

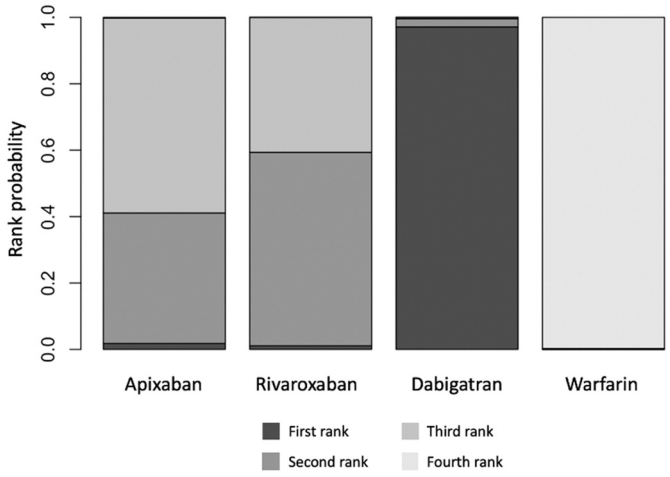

Fig. 4. Treatment rank probabilities for the lowest risk of acute kidney injury.

and safety of anticoagulation therapy in these patients – patients with advanced CKD were excluded from major clinical trials of DOACs in AF. Our systematic review further demonstrated a lack of representation of such individuals in real-world studies – the subgroup of patients with eGFR of 30 ml/min/1.73m^2 or below was evaluated in only two out of eight studies, with small sample sizes. More research is needed to generate high-quality evidence to guide anticoagulation therapy in this patient population.

Strengths of this study include the comprehensive evaluation of clinical trials and longitudinal studies across large, multinational populations, and a network meta-analysis approach to comparing individual oral anticoagulants which identified dabigatran as the DOAC potentially associated with the lowest AKI risk, and subgroup analyses in patients with existing mild-to-moderate CKD. This study also has limitations. First, all included studies for network meta-analysis were observational, subjecting our findings to residual confounding. Although most studies utilized inverse probabilities of treatment weighting based on propensity scores to minimize confounding-by-indication, the risk of bias remained high. The strength of evidence is overall low, rendering our network meta-analysis findings hypothesis-generating only. Second, most studies ascertained AKI using administrative codes which may have introduced under-reporting and misclassification bias. Third, data on medication dose were not available for all studies. However, the dosing of medications has been consistent between most clinical studies and real-world practice. Fourth, there were few data regarding edoxaban, limiting the evaluation of this medication in our analysis. The lack of representation of edoxaban in post-marketing studies may reflect its diminished favorability in clinical practice because of a potentially lower efficacy than warfarin due to high renal excretion in patients with creatinine clearance >95 ml/min.

5. Conclusions

This systematic review and network meta-analysis of studies in patients with atrial fibrillation found that AKI was common in long-term users of oral anticoagulants. Each individual DOAC, i.e., apixaban, rivaroxaban, and dabigatran, was associated with a lower risk of AKI compared to warfarin, with dabigatran associated with the lowest risk. Future research is needed to investigate whether this finding is attributable to pharmacologic properties of the medication, geolocation differences in clinical practice and patient populations, or confounding.

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None.

CRediT authorship contribution statement

Shengyuan Luo, Laith A. Derbas, Yumeng Wen: Conceptualization,

methodology, software, data curation, writing- original draft preparation.

Sally Arif, Melissa Tracy, Jeremiah Wasserlauf, Henry D. Huang: writing- reviewing and editing.

Jochen Reiser, Kim A. Williams, Annabelle Santos Volgman: Supervision.

Declaration of competing interest

Jochen Reiser is a cofounder and shareholder of Walden Biosciences. Annabelle Santos Volgman have the following disclosures: Sanofi (consulting), Pfizer (consulting), Bristol Myers Squibb Foundation Diverse Clinical Investigator Career Development Program (DCICDP) National Advisory Committee (NAC), Novartis and NIH Clinical Trials, Apple Inc. stock.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100132.

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