



**The Analysis Study of Clinical Benefits and Risk of Oral
Anticoagulant Therapy in Patient with Chronic Kidney Disease :
A Comprehensive Systematic Review**

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ABSTRACT

Background: Arterial hypertension and diabetes mellitus are the primary causes of Chronic kidney disease CKD, while CKD is recognized as an independent risk factor for the onset of CVD. The aim of this study to show about clinical benefits and risk of oral anticoagulant therapy in patient with chronic kidney disease. **Methods:** By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Scienedirect were used to do this. **Result:** Eight publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** Although there is a need for cardiorenal consensus regarding anticoagulation in CKD, adequate selection of the anticoagulant type and careful monitoring are some extremely useful indications for overcoming management challenges.

Keyword: Chronic kidney disease, oral anticoagulant, benefit, management.

INTRODUCTION

The number of patients with CKD and patients with ESKD is increasing in the United States on the basis of the National Health and Nutrition Examination Survey data from 1999 to 2014. Although heart failure, thrombotic cardiovascular events, and sudden cardiac death are common in CKD and ESKD, this population is also at a disproportionately higher risk of nonvalvular atrial fibrillation (AF) compared with the general population. Prevalence of AF increases as kidney disease worsens, and it is close to 15% by the time that patients with CKD become dialysis dependent, which is more than three times that of age-matched controls. Use of oral anticoagulants is common, and these agents are among the top 15 drugs prescribed to patients with CKD and patients with ESKD enrolled in Medicare Part D, Medicare Advantage, or Managed Care prescription drug programs.^{1,2}

Patients with chronic kidney disease have an increased risk of

venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism. Patients with chronic kidney disease (CKD) stage 3 and 4 (eGFR 30–60 and eGFR15–29 ml/min/1.73 m²) have an adjusted relative risk 1.71 (95% CI 1.18 to 2.49) of developing DVT compared to those with normal renal function. The risk is further heightened in those on dialysis where the age-adjusted pulmonary embolism incidence ratio is 2.34 compared to those with normal renal function. With hospital-acquired VTE being a potentially preventable cause of in-hospital mortality the increased risk of VTE also highlights the need for appropriate VTE prophylaxis in a CKD population. Patients with CKD are also at increased risk of developing atrial fibrillation (AF) which may predispose them to thromboembolic stroke (ischaemic stroke). The prevalence of AF in the general population is estimated at around 1–2%, this rate is reported to be much higher as renal function

declines, with reports of up to 10–25% of patients on dialysis.^{3,4}

Both atrial fibrillation and venous thromboembolism (VTE) are highly prevalent among patients with chronic kidney disease (CKD). Until recently, warfarin was the most commonly prescribed oral anticoagulant. Direct oral anticoagulants (DOACs) have important advantages and have been shown to be noninferior to warfarin with respect to stroke prevention or recurrent VTE in the general population, with lower bleeding rates. This review article will provide available evidence on the use of DOACs in patients with CKD.^{5,6}

Patients with CKD are not only at a higher risk of thrombosis, they are also at increased risk of bleeding. Furthermore, the pharmacokinetics and pharmacodynamics of many anticoagulant therapies are significantly affected by renal dysfunction. In addition, patients with advanced CKD are often systematically excluded from major clinical trials. As such, the decision on whether to anticoagulate or not, and if so with what agent, poses

significant challenges. A solid understanding of the condition in question and the available treatments is required to make an informed judgement call. An in-depth appreciation of the advantages and disadvantages of the currently available anticoagulants is a key element in the decision-making process.^{7,8}

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast clinical benefits and risk of oral anticoagulant therapy in patient with chronic kidney disease. It is possible to accomplish this by researching of clinical benefits and risk of oral anticoagulant therapy in patient with

chronic kidney disease. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about clinical benefits and risk of oral anticoagulant therapy in patient with chronic kidney disease. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " clinical benefits and risk of oral anticoagulant therapy in patient with chronic kidney disease." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases by inputting the words: *((("Chronic kidney disease"[MeSH Subheading] OR " Oral anticoagulant"[All Fields] OR "Kidney injury" [All Fields]) AND ("Therapy"[All Fields] OR "Risk factor"[All Fields]) AND ("Management"[All Fields]) OR ("Benefit oral anticogulant" [All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All

submissions need to be written in English and cannot have been seen anywhere else.

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract

before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

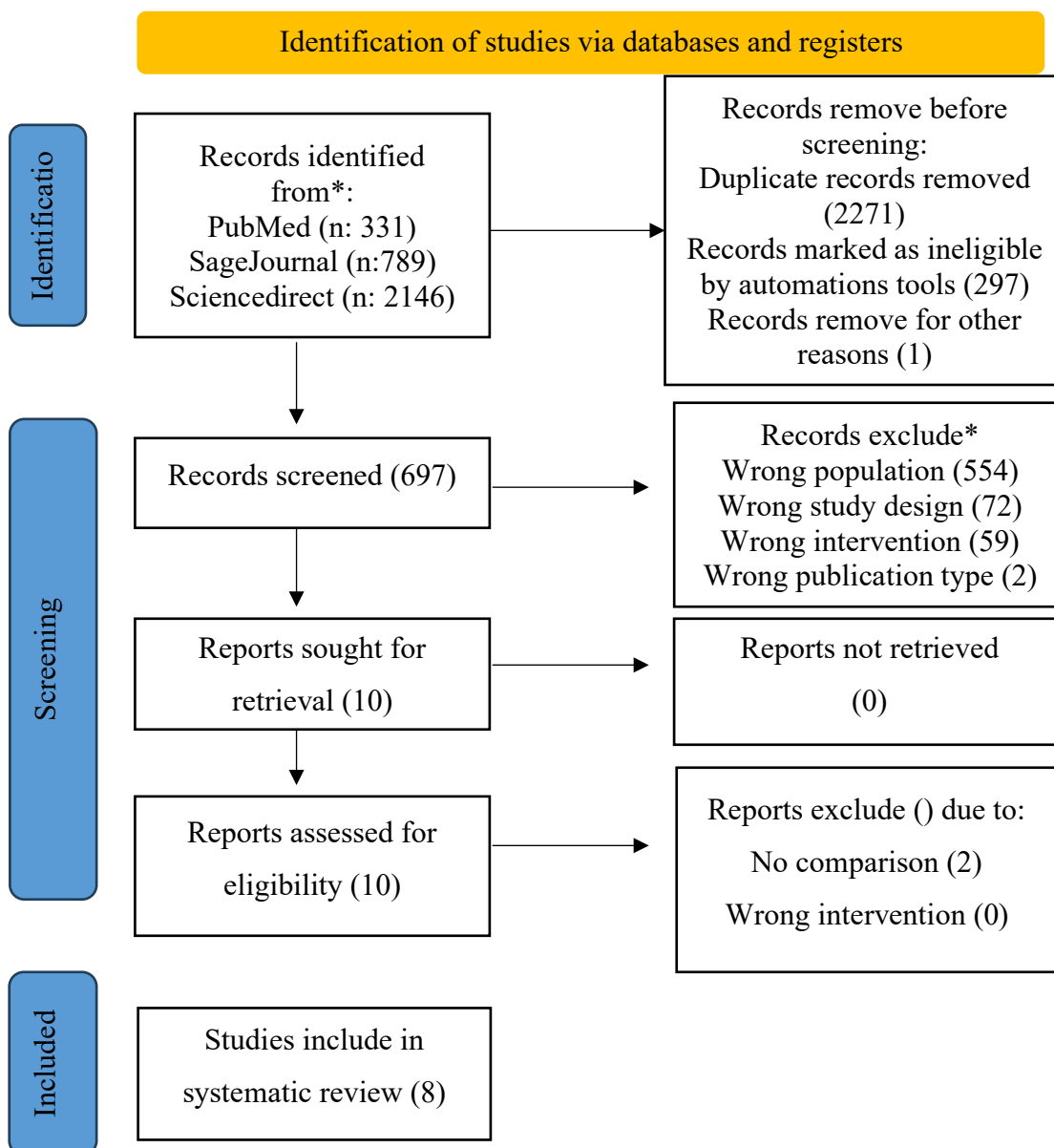


Figure 1. Article search flowchart

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 3266 publications. A thorough three-level screening strategy was used to identify only eight papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Cho, MS et al., 2023 ⁹	Republic of Korea	This is a retrospective observational review of patients with AF who were managed at Asan Medical Center (Seoul, Korea) between January 1, 2006, and December 31, 2018.	12714	We identified 12,714 consecutive patients with AF (mean 64.6 ± 11.9 years, 65.3% male, mean CHA ₂ DS ₂ -VASc score 2.4 ± 1.6 points) between 2006 and 2017. In patients receiving anticoagulation therapy (n=4447, 35.0%), warfarin (N=3768, 84.7%) was used more frequently than NOACs (N=673, 15.3%). There was a higher 3-year rate of NACE with renal function deterioration (14.8%, 18.6%, 30.3%, 44.0%, and 48.8% for CKD stages 1–5, respectively). The clinical benefit of anticoagulation therapy was most prominent in patients with CKD 1 (hazard ratio [HR] 0.49, 95% confidence interval [CI] 0.37–0.67), 2 (HR 0.64 CI 0.54–0.76), and 3 (HR 0.64 CI 0.54–0.76), but not in CKD 4 (HR 0.86, CI 0.57–1.28) and 5 (HR 0.81, CI 0.47–1.40). Among patients with CKD, the benefit of anticoagulation therapy was only evident in those with a high risk of embolism (CHA ₂ DS ₂ -VASc score ≥ 4 , HR 0.25, CI 0.08–0.80).

Montomoli,M et al., 2022 ¹⁰	Spain	The FAERC study performed a retrospective multicentre analysis of historical cohorts in which data were collected from arrhythmia diagnosis onwards.	4749	We analysed a Spanish cohort of 4749 patients with CKD (mean eGFR 33.9 mL/min) followed up in the nephrology clinic, observing a 12.2% prevalence of non-valvular AF. In total, 98.6% of these patients were receiving anticoagulant treatment, mainly with coumarins (79.7%). Using direct-acting oral anticoagulants (DOACs) was associated with fewer cerebrovascular events than using acenocoumarol, but in contrast with other studies, we could not corroborate the association of risk of bleeding, coronary events, or death with a type of anticoagulant prescribed.
Yao, X et al., 2020 ¹¹	US	Using a US administrative claims database with linked laboratory data, 34,569 new users of oral anticoagulants with AF and eGFR ≥ 15 mL/min/1.73 m ² were identified between 10/1/2010–11/29/2017.	34569	In comparison to warfarin, apixaban was associated with a lower risk of stroke (hazard ratio [HR] 0.57 [0.43–0.75]; $p < 0.001$), major bleeding (HR 0.51 [0.44–0.61]; $p < 0.001$), and mortality (HR 0.68 [0.56–0.83]; $p < 0.001$); dabigatran was associated with a similar risk of stroke but a lower risk of major bleeding (HR 0.57 [0.43–0.75]; $p < 0.001$) and mortality (HR 0.68 [0.48–0.98]; $p = 0.04$); rivaroxaban was associated with a lower risk of stroke (HR 0.69 [0.51–0.94]; $p = 0.02$), major bleeding (HR 0.84 [0.72–0.99]; $p = 0.04$), and mortality (HR 0.73 [0.58–0.91]; $p = 0.006$). There was no significant interaction between treatment and eGFR categories for any outcome. When comparing one NOAC to another NOAC, there was no significant difference in mortality, but some differences existed for stroke or major bleeding. No relationship between treatments and

				falsification endpoints was found, suggesting no evidence for substantial residual confounding.
Park, H et al., 2023¹²	Korea	Using data from the COMparison study of Drugs for symptom control and complication prEvention of AF (CODE-AF) registry, 260 non-valvular AF patients with advanced CKD (defined as estimated glomerular filtration rate <30 mL/min per 1.73/m ²) or ESRD on dialysis were enrolled from June 2016 to July 2020.	260	During a median 24 months of follow-up, major or CRNM bleeding risk was significantly reduced in the DOAC group compared to the warfarin group [hazard ratio (HR) 0.11, 95% confidence interval (CI) 0.01 to 0.93, $p=0.043$]. In addition, the risk of composite adverse clinical outcomes (major or CRNM bleeding, stroke/SE, myocardial infarction/CLI, and death) was significantly reduced in the DOAC group compared to the no OAC group (HR 0.16, 95% CI 0.03 to 0.91, $p=0.039$).
Vestergaard, AEF et al., 2024¹³	Denmark	We conducted a cohort study including patients initiating oral anticoagulant treatment within 3 months after an atrial fibrillation diagnosis in Denmark during 2012–18.	32781	We included 32 781 persons with atrial fibrillation initiating oral anticoagulation (77% initiating DOACs). The median age was 75 years, 25% had a baseline estimated glomerular filtration rate <60 mL/min/1.73 m ² , and median follow-up was 2.3 (interquartile range 1.1–3.9) years. The weighted 1-year risks of AKI were 13.6% in DOAC users and 15.0% in VKA users (HR 0.86, 95% CI 0.82; 0.91). The weighted 5-year risks of CKD progression were 13.9% in DOAC users and 15.4% in VKA users (HR 0.85, 95% CI 0.79; 0.92). Results were similar across subgroups and in the per-protocol analysis.
Bo, D et al., 2023¹⁴		A retrospective study.	19672	After PSM, 2042 pairs of AKI and AF patients were matched between the patients who received OAC and those without anticoagulant treatment. Cox regression analysis showed that,

				OAC significantly reduce 30-day mortality compared with non-OAC (HR 0.30; 95% CI 0.25 to 0.35; p<0.001). Linear regression analysis revealed that OAC prolong LOS in hospital (11.3 days vs 10.0 days; p=0.013) and ICU (4.9 days vs 4.4 days; p<0.001). OAC did not improve survival in patients with haemorrhage (HR 0.67; 95% CI 0.34 to 1.29; p=0.23). Novel OAC did not reduce mortality in acute-on-chronic renal injury (HR 2.03; 95% CI 1.09 to 3.78; p=0.025) patients compared with warfarin.
Calderon, JM et al., 2022 ¹⁵	Spain	The data generated during the study was handled according the Spanish Law 3/2018 of Data Protection and Guaranty of Digital Rights the and corresponding European norms	65734	A total of 65,734 patients with AF, mean age 73.3 ± 10.49 years old and 47% females and follow-up of 3.2 years were included. KDIGO classification were: G1 33,903 (51.6%), G2 17,456 (26.6%), G3 8024 (12.2%) and G4 6351 (9.7%). There were 8592 cases of stroke and TIA, 437 intracranial hemorrhage, and 9603 all-cause deaths (incidence 36, 2 and 38 per 10 ³ person/year, respectively). 4.1% of patients with CHA2DS2-VASc Score 2 or higher did not receive anticoagulant therapy. Risk of stroke, TIA, and all-cause mortality increased from G1 to G4 groups. Anticoagulant treatments reduced the risk of events in the four categories, but NOAC seemed to offer significantly better protection. Renal dysfunction increases the risk of events in AF and anticoagulant treatments reduced the risk of stroke and all-cause mortality, although NOAC were better than VKA.

Ha, JT et al., 2023 ¹⁶	Australia	Multicenter retrospective cohort.	55568	55,568 patients (27,784 rivaroxaban–warfarin user matched pairs; mean age 74 years, 46% female, 33.5% with eGFR <60 mL/min/1.73 m ²) experienced a total of 4,733 (8.5%) effectiveness and 1,144 (2.0%) bleeding events. Compared to warfarin, rivaroxaban was associated with greater or similar effectiveness across a broad range of kidney function (pooled HRs of 0.72 [95% CI, 0.66-0.78], 0.78 [95% CI, 0.58-1.06], 0.70 [95% CI, 0.57-0.87], and 0.78 [95% CI, 0.62-0.99]) for eGFR ≥60, 45-59, 30-44, and <30 mL/min/1.73 m ² , respectively). Rivaroxaban was also associated with similar risk of major bleeding across all eGFR categories (pooled HRs of 0.75 [95% CI, 0.56-1.00], 1.01 [95% CI, 0.79-1.30], 0.87 [95% CI, 0.66-1.15], and 0.63 [95% CI, 0.37-1.09], respectively).
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DISCUSSION

The presence of chronic kidney disease (CKD) increases both thromboembolic and bleeding risks in patients with atrial fibrillation (AF), which makes anticoagulation therapy challenging in this patient group. Although the introduction of direct oral anticoagulants (DOACs) has led to safer oral anticoagulation (OAC) therapy in general, there are areas of uncertainty in patients with AF and

CKD. Notably, patients with advanced CKD [creatinine clearance (CrCl) <30 mL/min] have been excluded from the pivotal randomized controlled trials (RCTs), except for some patients on apixaban with CrCl of 25–30 mL/min. In addition, few studies have directly compared DOACs in patients with CKD.^{17,18}

Oral anticoagulants (OACs) used in CKD do not differ from those used in general practice and are represented by vitamin K antagonists

(VKAs) and direct OACs. However, their pharmacokinetic and pharmacodynamic features require the adjustment of therapeutic regimens. VKAs are still the most widely used, with the mention that is the warfarin for which the majority of clinical evidence was obtained. AF guidelines recommend warfarin differently in CKD. The American Guidelines American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommend warfarin in all CKD stages (stages 2–3—Class I, Level of Evidence (LOE) A, stage 4—Class IIb, LOE C, stage 5—Class IIa, LOE B). The Canadian Guidelines prefer warfarin in stage 4, and the European Society of Cardiology (ESC) guidelines do not provide specific information for a particular type of OAC in any CKD stage. Although the guidelines for AF or VTE do not recommend drug dose adjustment in CKD.^{19,20}

Chronic kidney disease is defined as the presence of abnormal kidney function or structure for more than 3 months. It is classified according to the categories of

estimated glomerular filtration rate (eGFR), which ranges from CKD stage 1 (normal eGFR ≥ 90 mL/min/1.73 m², but the presence of albuminuria, haematuria, a pathological abnormality or a structural abnormality) to CKD stage 5 (end stage kidney disease, eGFR < 15 mL/min/1.73 m² and/or patient on dialysis).^{21,22}

Direct oral anticoagulants (DOACs) include factor Xa inhibitors and direct thrombin inhibitors (DTI). The former inhibits both the direct and indirect coagulation pathways by occupying the active site of the factor Xa molecule. DTI, as its name implies, acts directly on the prothrombin transformation process to prevent fibrin formation. Vitamin K antagonists (VKA) exert their pharmacological function by inhibiting vitamin K epoxide reductase (VKOR). This enzyme catalyzes the conversion of vitamin K to dihydroquinone, which is required for glutamic acid carboxylation.^{23,24}

Previous meta-analyses have revealed that, compared with warfarin, using DOACs is linked to a lower risk of developing AKI.

However, due to differences in the action mechanisms of these drugs, it might be inappropriate to evaluate their renal outcomes together. The drugs in the DOACs group were analyzed separately in this systemic review to provide clinicians with more accurate guidance when deciding which oral anticoagulants should be given to patients with NVAf who require anticoagulation therapy.^{23,25}

CONCLUSION

Although there is a need for cardio-renal consensus regarding anticoagulation in CKD, adequate selection of the anticoagulant type and careful monitoring are some extremely useful indications for overcoming management challenges.

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