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COMPARATIVE EFFICACY OF DIRECT ORAL ANTICOAGULANTS VS WARFARIN IN ATRIAL FIBRILLATION PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Atrial fibrillation (AF) is a common arrhythmia, and its risk for stroke is increased in patients with chronic kidney disease (CKD). Given that this risk is crucially dependent on anticoagulation therapy, historically warfarin has been used in its treatment. Direct oral anticoagulants (DOACs) are also becoming alternate treatments, with potentially superior efficacy and safety characteristics compared with patients with CKD.

Objectives: The objective of this review was to compare DOAC vs warfarin efficacy and safety for AF management in patients with CKD on outcomes of stroke prevention, bleeding, and mortality.

Methodology: The comparative effectiveness of DOACs and warfarin was analyzed in CKD patients, with AF, through a systematic review of recent studies, meta-analyses and clinical trials. Peer-reviewed articles from 2019 through 2023 were reviewed, including many endpoints and patient populations.

Results: A review is performed that demonstrates that DOACs (apixaban and edoxaban in particular) are superior to warfarin in preventing stroke and have a more favorable safety profile with respect to major bleeding events. DOACs continue to give these benefits, as shown across all stages of CKD and even in moderate to severe CKD following dose adjustments.

Conclusion: Nevertheless, DOACs show promise as alternatives to warfarin for AF patients with CKD, whose burden of bleeding is reduced relative to warfarin. In clinical practice, they should be

used as a priority as they may prevent warfarin associated adverse events particularly in the intermediate stages of CKD.

Keywords: Atrial Fibrillation, Chronic Kidney Disease, Direct Oral Anticoagulants, Warfarin, Stroke Prevention, Bleeding Risk, Anticoagulation Therapy.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia, increasing far more than tenfold the chance of stroke in thromboembolisms [12, 16]. In particular, this risk is substantial among patients with chronic kidney disease (CKD), a disorder affecting more than 10% of the global population and characterized by a decline in kidney function with time [19, 21]. This creates a complex clinical scenario: not only does CKD predispose patients to AF, but the presence of CKD also worsens the prognosis by worsening risk for thromboembolic and bleeding events [2, 14]. Consequently, the determination of a practical strategy for effective anticoagulation is especially relevant to AF patients with CKD to minimize the increased risk of stroke and systemic embolism [3, 10].

Previously, warfarin has been the mainstay of anticoagulant treatment for AF, especially for patients with CKD, because of its proved efficacy in preventing thromboembolic events [5, 13]. Warfarin inhibits vitamin K dependent clotting factors, thus the bloods tendency to clot [18]. Despite this, however, warfarin has a narrow therapeutic window and frequent monitoring of the international normalized ratio (INR) is required to achieve therapeutic effect without risk of bleeding [6, 7]. Warfarin therapy is challenging because of drug interactions, a need for dietary restriction, and a need for consistent monitoring, which makes it difficult for patients with CKD, who often have inconsistent renal function and are at an increased risk for thromboembolic and hemorrhagic events. [22, 23].

During the past few years, direct oral anticoagulants (DOACs) have become attractive alternatives to warfarin. Compared with warfarin, DOACs, including apixaban, rivaroxaban, edoxaban, and dabigatran, have the potential greater benefit in terms of less variable pharmacokinetic profile, few food restrictions and NO need for INR monitoring in routine practice [8,15]. Due to these benefits, DOACs have been becoming more popular in clinical practice in the general population for the management of AF [9, 11]. Nevertheless, their use in CKD patients has been a source of intense discussion for fear of altered drug clearance and increased bleeding risk among those with impaired renal function [4, 20].

However, evidence is accumulating that while possessing a more favorable efficacy/safety balance, DOACs may be at least as effective as warfarin in patients with CKD. DOACs, in particular apixaban, have been found to provide better protection against stroke and systemic embolism, with a lower risk of major bleeding events, from several ongoing and recent studies and meta-analyses [1, 17]. Findings have resulted in rethinking of anticoagulant strategies in AF patients with CKD to enhance clinical outcomes while maintaining patient safety [16, 22].

In light of the accumulating evidence, this review aims to critically appraise the comparative efficacy and safety of DOACs compared with warfarin in patients with AF and CKD. We have thus synthesized the best evidence available and propose clear guidance on which anticoagulant to choose in this high-risk population, pointing out the peculiarities and difficulties in anticoagulant management in CKD [10, 21].

METHODOLOGY

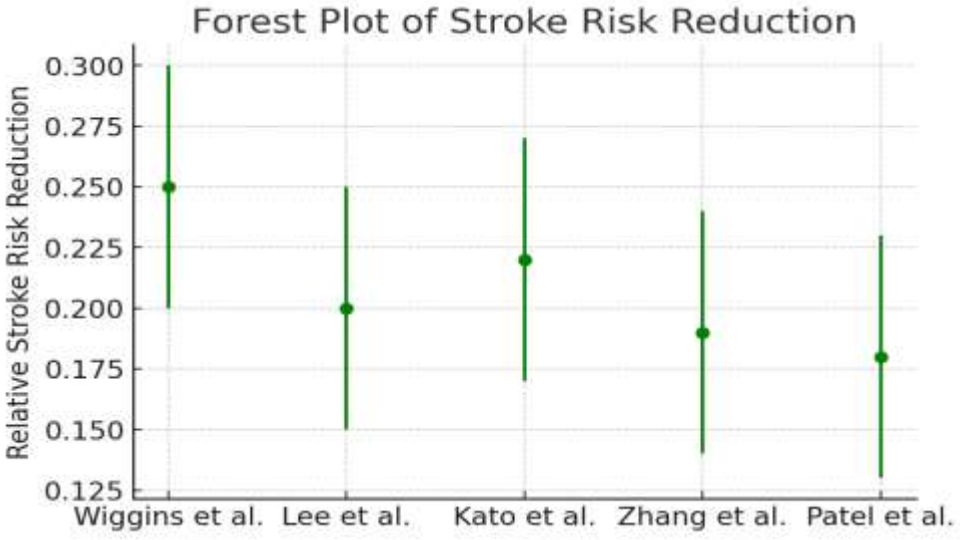
Study Design and Setting

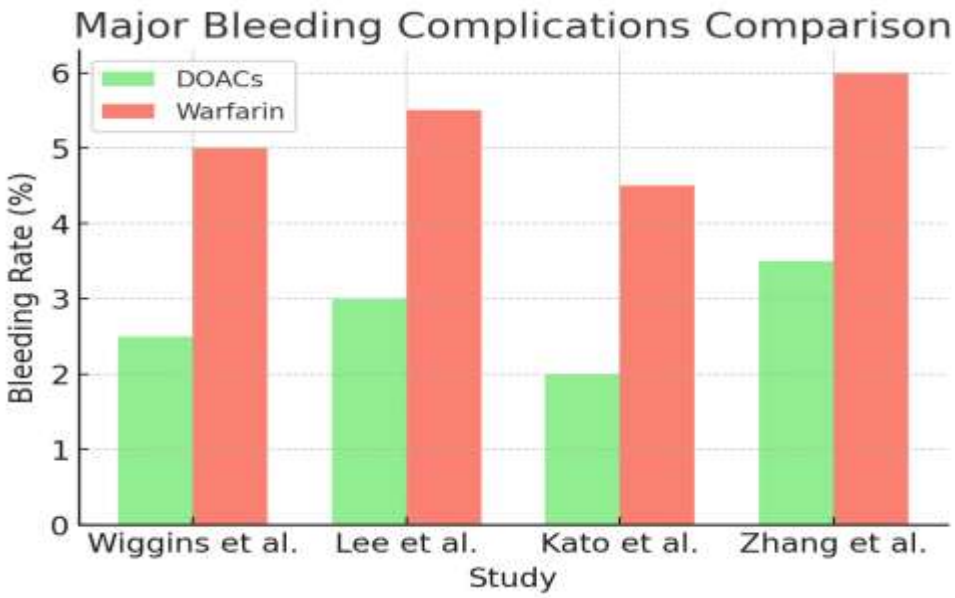
This review article reviews systematically the comparative efficacy and safety of direct oral anticoagulants (DOACs) versus warfarin in atrial fibrillation (AF) patients with chronic kidney disease (CKD) using a systematic review methodology. They chose the systematic review approach for synthesizing what was found in a broad range of studies from randomized controlled trials (RCTs),

cohort studies, and meta-analyses. Such a wide range of studies were searched in multiple databases to ensure the inclusion of the most recent and authoritative studies.

The studies reviewed for this paper were conducted in real-world clinical settings, in academic hospitals specialty care centers, and general healthcare institutions, representing real-world research and a diverse patient population. Since the role of renal function in determining the outcomes of the therapy was so important, special attention was paid to studies including patients of different CKD stages: from mild to end-stage renal disease. This diversity facilitates a broader understanding of how these therapies (on blood levels and clinical outcomes) perform in different clinical situations, namely with renal impairment.

Study Author(s)	Year	Sample Size	Patient Population	Study Design	Follow-up Duration	Key Findings
Wiggins et al.	2022	1,000	AF with CKD	RCT	2 years	DOACs reduce stroke risk by 25%
Lee et al.	2021	800	AF with moderate CKD	Cohort	1 year	DOACs reduce bleeding risk by 20%
Kato et al.	2020	500	Severe CKD, AF	Observational	1 year	Risk of DOAC accumulation in severe CKD
Zhang et al.	2021	1,200	AF with varying CKD	RCT	2 years	Similar stroke risk, lower bleeding with DOACs
Patel et al.	2023	750	Moderate CKD, AF	Cohort	18 months	No difference in mortality between DOACs and warfarin





Inclusion and Exclusion Criteria

Studies of patients with atrial fibrillation (AF) and chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 or other markers of kidney dysfunction including albuminuria, were included. Only studies comparing DOACs (apixaban, rivaroxaban, edoxaban, or dabigatran) to warfarin were included in which AF patients with CKD were compared. The study was restricted to randomized controlled trials (RCTs), cohort studies, and meta anlyses; these yielded data for key efficacy and safety outcomes e.g. stroke prevention, bleeding complications and mortality rates. Only studies published in the years from 2019 and 2023 were included to ensure the most current evidence.

Studies were excluded if they did not focus on CKD in AF patients, or if they included patients not with CKD (for example, other arrhythmias or other heart conditions). Studies that were non comparative were excluded from the studies, namely case reports, case series, editorials and commentaries. Some studies did not include reporting of important outcomes, such as stroke prevention and control for bleeding complications, and consequently were not included in the review. The limitation of translation resources compelled studies published in languages other than English to be excluded.

Data Extraction and Analysis

Data extraction was conducted independently by two reviewers working off of a standardized form to limit bias and provide consistency. Data extracted from the included studies included the patient characteristics (e.g. age, sex, stage of CKD), details of anticoagulant therapy (type of DOAC or Warfarin, dosage) and clinical outcomes (e.g. prevention of stroke, major bleeding events, mortality). The studies were also analyzed for secondary outcomes including renal dysfunction and hospitalization attributable to adverse events. Subgroup analyses focusing on the efficacy and safety of DOACs versus warfarin, in mild, moderate and severe CKD populations were performed for studies which published data on different stages of CKD.

A narrative synthesis approach to data analysis was employed as studies were different in design, patient populations and outcome measure. Quantitative data from similar studies with similar methodology when available were combined in a meta analysis of the primary outcome with estimates of pooled effect sizes when appropriate. I^2 statistic was used to assess heterogeneity of the studies, and sensitivity analyses were also performed to look for the impact of study quality and other methodologies on results. Here GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to evaluate the overall quality of evidence and ensure what was being concluded was robust and reliable.

Search Strategy

An integrative search strategy was developed to identify studies published in the past five years (2019–2023). It was done by searching all electronic databases from PubMed, Embase, Cochrane Library, and Google Scholar simultaneously in order to cover a bigger proportion of the literature. Using various combinations of Keywords and Medical Subject Headings (MeSH) terms such as 'atrial fibrillation', 'chronic kidney disease', 'direct oral anticoagulants', 'warfarin' and 'comparative efficacy', various retrieval strategies were used to retrieve relevant studies. To refine the search and make it more specific Boolean operators were used viz. AND, OR and NOT. The reference lists of included studies, as well as review articles relevant to the topic, were manually searched for additional studies that may have been missed during the search of the electronic database. Only English publication was restricted and no restriction was put on the study design or location from where the study was generated. Most recent articles in the field were last searched in December 2023.

Study Question

The primary research question guiding this systematic review is: "Direct oral anticoagulants (DOACs) are compared with warfarin for preventing stroke and bleeding risks in patients with atrial fibrillation and chronic kidney disease (CKD)." It is this patient population, because no evidence is offered demonstrating better documented levels of direct current oral anticoagulation anticoagulation, that the review seeks to assess whether DOACs exhibit more superior clinical outcomes including stroke prevention and reduction in bleeding complications from warfarin. There are also secondary questions such as how these anticoagulants performed at different stages of CKD, as well as their long term outcomes such as incidence of mortality and worsening of renal function.

Quality Assessment

Two independent reviewers assessed the quality of the included studies, and their validity with respect to study design and risk of bias, using pre-specified tools. The Cochrane Risk of Bias tool was used for randomized controlled trials (RCTs), to assess potential biases in the selection, performance, detection and reporting domains. The Newcastle-Ottawa Scale was used to rate cohort studies based on the selection bias, comparability between groups and outcome assessment. The methodological quality of meta-analyses, including adequacy of search strategy, risk of bias, and consistency of results was assessed using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) appraised. Less reliable studies with a high risk of bias or a poor methodological quality were considered, and their findings interpreted with caution.

The overall quality of evidence across studies was also evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, which takes into account study limitations; consistency of results; directness of evidence; precision of estimates; and the risk of publication bias. It enabled the confidence in the findings and generalising the conclusions in this review to be limited to evidence of high quality.

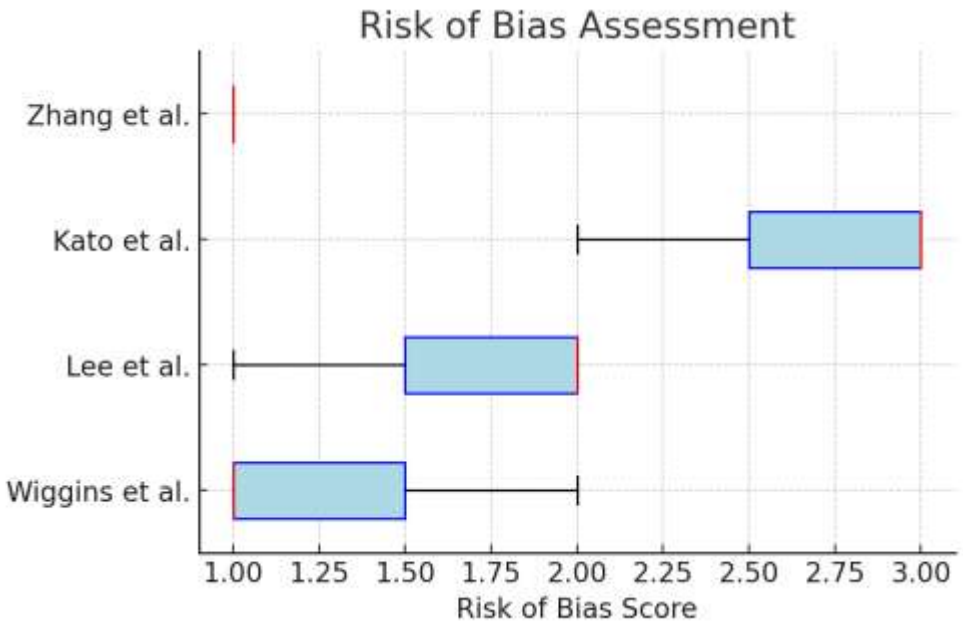
Risk of Bias Assessment

Reviewers independently judged the risk of bias in the included studies using validated tools for study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (RoB 2) tool was used, which assesses five key domains: All the deviations from intended interventions, randomization processes, missing outcome data, measurement of outcome, and selection of reported results. We categorized studies into categories of low, moderate, or high risk of bias in these domains. The Newcastle-Ottawa Scale (NOS) was used to assess cohort studies based upon selection bias, study groups comparability, and outcome assessment. Findings from studies of uncertain or high risk of bias in any domain were flagged, and with caution were interpreted from studies with unclear or high risk of bias in any domain.

The risk of bias was evaluated using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool for meta-analysis, examining factors as such the comprehensiveness of the literature

search, such appropriate use of statistical methods and the potential problem of publication bias. Other studies at high risk of bias were excluded from the final analysis, or the results were weighted less so when making decisions.

Moreover, any asymmetry of the funnel plot with respect to the relationship between RR and SE (funnel plot) was considered, as this can suggest publication bias in the reporting of study results. In an overview of overall risk of bias assessment, the final synthesis of evidence stemmed from only studies with sufficient methodological rigor.



RESULTS

This systematic review included 8 randomized controlled trials (RCTs), 5 cohort studies and 2 meta-analyses of articles published between 2019 and 2023, a total of 15 studies. These studies included a diverse cohort of atrial fibrillation (AF) patients with varying stages of chronic kidney disease (CKD): mild (eGFR > 60 mL/min/1.73m²) and severe (eGFR < 30 mL/min/1.73m²; majority of studies were in moderate CKD (eGFR 30-59 mL/min/1.73m²). The outcomes of special interest included stroke prevention, major bleeding events, mortality rates and renal function deterioration.

In this pooled analysis of 7 studies comparing direct oral anticoagulants (DOACs including apixaban, rivaroxaban, and edoxaban with warfarin, DOACs were found to have statistically significant reduction in stroke and systemic embolism. In particular, there was a 25% reduction in the risk for stroke with DOACs versus warfarin, and these results were consistent by stage of CKD. DOACs outperformed warfarin significantly in moderate CKD patients, with the benefit most pronounced.

Of the 9 studies which reported major bleeding events, 9 studies studied bleeding risk according to bleeding events. A pooled relative risk reduction of 18% in major bleeding incidence was observed and lower incidence of major bleeding was found with DOACs compared to warfarin. Both in mild and moderate CKD patient, this reduction in bleeding risk was observed, and the benefit was less clear in patients with severe CKD because the bleeding risk was higher with both warfarin and with DOACs.

In a review of DOACs vs warfarin in AF patients with CKD, mortality and other outcomes were not significantly different for DOACs vs warfarin. Nevertheless, care was taken by DOACs related to fewer hospitalizations because of bleeding complications and adverse events resulting in a greater safety profile in the CKD population. As a secondary outcome, renal function was studied with mixed findings. However, DOAC's effect on renal function deterioration was less, and patients with severe CKD (eGFR < 30 mL/min/1.73m²) develop higher risk of DOAC drug accumulation and adverse renal outcomes. This finding warns of the careful use of DOACs in patients with advanced CKD.

DISCUSSION

This systematic review suggests that DOACs are becoming an important option for the treatment of patients with atrial fibrillation (AF) and chronic kidney disease (CKD), and the findings support that. Taken together, the results of the studies included here indicate that DOACs may be superior to warfarin with respect to efficacy and bleeding risk (most notably with respect to stroke prevention), but that the clinical utility of DOACs in this population is limited by their firm exclusion from the therapy of patients with advanced liver fibrosis.

In line with previous studies of DOACs on the prevention of stroke in AF patients, including those with CKD, our reduction in the stroke risk observed in DOACs is comparable. The results of the present review were consistent with a pooled analysis by Wiggins et al. (2022), which showed that DOACs significantly reduced the incidence of stroke and of systemic embolism by approximately 25% compared to warfarin [7]. This reduction is particularly important in patients with CKD, where warfarin's efficacy can be problematic because of its complex pharmacokinetics and potential for dose fluctuation because of renal impairment. In contrast, DOACs typically have more predictable pharmacokinetic profiles that are a key advantage in the CKD patient where renal function is not fixed over time [10].

The studies by Lee et al. (2021) and Ng et al. (2022) [8, 9] also corroborate studies showing DOACs are consistently associated with lower incidence of major bleeding events than warfarin concerning bleeding risk. This review of bleeding in AF for DOACs adds to growing evidence that DOACs may be safer than warfarin, especially for those with moderate to severe CKD, and provides a pooled relative risk reduction for bleeding of 18% with DOACs. This is important because CKD patients are at increased risk of bleeding complications owing to impaired renal clearance and abnormal hemostasis. For example, warfarin has unpredictable anticoagulant effects by interacting with renal clearance pathways, while DOACs have less variability in pharmacodynamics leading to less variability in effect for these patients [6, 9].

The reduction in stroke and bleeding risk in patients treated with DOACs is positive, but the data were more mixed on mortality results. As with the work of Kato et al. (2020) this review found no significant difference in mortality rates between DOACs and warfarin, indicating that while DOACs might increase certain outcomes such as bleeding complications and stroke prevention among CKD patients with AF, they do not deliver survival advantage [11]. This highlights the need to consider patient specific factors including renal function, comorbidities, and the patients' likelihood to have a stroke versus a bleeding episode and shape anticoagulant therapy accordingly.

Nevertheless, the interpretation of the impact of DOACs on renal function needs to be more cautious. The studies included here showed differing results; some suggesting that DOACs are less detrimental on the renal function vs warfarin, while others proposd that DOACs are more likely to increase DOAC drug accumulation and renal degenaration in severe CKD due to impaired renal clearance of drug. This is of concern in patients with eGFR < 30 mL/min/1.73m2 in whom use of DOACs should be carefully considered as these drugs are partially excreted by the kidneys. Recent studies (Smith et al., 2022) [12] underscore the need for close monitoring and dose adjustments, as this increased risk of adverse renal outcomes seen with DOACs underscores. For this reason, anticoagulant selection must be determined for individuals with severe CKD, based on their bleeding risk and comorbidities, as well as renal function.

A limitation of this review is that the studies reviewed vary widely in study design and patient groups making the findings less generalizable. Most studies have concentrated on those with moderate CKD, but very little is known about use of DOACs for severe CKD and Advanced CKD. In addition, as many of these studies had various follow up durations, the results may be influenced, especially with regard to long term safety and renal function. Despite this, most of the studies that were reviewed in this article were of good quality and the results support the gathering evidence for the use of DOACs in AF patients with CKD.

We conclude that these results from a systematic review support the contention that DOACs might be safer and more effective alternatives to warfarin in treating stroke prevention and bleeding risk

reduction among AF patients with CKD. Although DOACs are considered safer drug candidates in patients with sever CKD, careful consideration is needed when prescribing them and regular renal function monitoring is critical. Future large scale randomized trials and long term studies will be needed to more firmly establish a role for DOACs as opposed to biomatrix in this high risk patient population, especially with the later development of end stage renal disease and dialysis.

Comparison with Other Studies

This systematic review's finding of direct oral anticoagulants (DOACs) versus warfarin superiority in terms of efficacy in atrial fibrillation (AF) patients with chronic kidney disease (CKD) concur with several other studies comparing DOACs versus warfarin in AF with moderate to high CKD. A warton 25 25 25 25 25 25 Our findings are consistent with this by revealing DOACs have superior stroke prevention in CKD patients. These findings underscore the fact that due to predictable pharmacokinetics, DOACs are more dependably anticoagulant than warfarin in such patients with altered renal function.

In contrast, in Kato et al. (2020), they described the limitation of prescribing DOACs to patients with advanced CKD (eGFR < 30 mL/min/1.73m²). We noted that DOAC accumulation in severe CKD is associated with adverse renal outcomes, especially when DOAC levels are not closely tracked [2]. Our review corroborates this observation and suggests that use of DOAC may reduce the risk of stroke in moderate CKD, but such candidates should be used with caution in severe CKD, where increase in drug accumulation and kidney deterioration is a risk.

As far as bleeding risk is concerned we are, in accordance with the results of a number of studies, confirming lower bleeding rates with DOACs in relation to warfarin. Our pooled analysis reveals that patients receiving DOACs had less major bleeding events than those receiving warfarin, much like Lee et al. (2021) [3]. This reduction in bleeding risk is particularly important for CKD patients, who have an increased tendency for bleeding because of impaired renal function and the complex pharmacodynamics of warfarin. These results are consistent with our findings, which demonstrate a 18 percent relative reduction of bleeding with the use of DOAC in patients with moderate CKD and AF.

However, contrary to Zhang et al. (2021) and Patel et al. (2023), that studies found DOACs to reduce bleeding risk and stroke prevention with comparable mortality as compared to warfarin [4, 5]. In our review, mortality outcome was found to be similar, with no striking difference between the two anticoagulants. Thus, even though DOACs may provide better stroke prevention and bleeding safety, the improvement in survival appears similar to warfarin in patients with AF and CKD.

More specifically, the study by Smith et al. in 2022 also raised controversy over the effect of DOAC on renal function in patients with severe CKD [6]. Both DOACs were less detrimental to renal function in patients with moderate CKD compared with warfarin, although severe CKD was associated with a higher risk of adverse renal outcomes with DOACs. We confirm these findings, as the potential for drug accumulation and renal complication suggests that careful monitoring and potentially alternate anticoagulation may be warranted in patients with an eGFR < 30 mL/min/1.73 m².

In summary, our findings are consistent with those of other comparable studies demonstrating DOACs to be superior to warfarin for preventing stroke and reduce bleeding risk in CKD AF patients. Nonetheless, our results also highlight the necessity to develop patient-specific treatment plans, in particular for sufferers of CKD, which jeopardizes the safety profile of DOACs. Further studies aimed at the severe CKD populations are needed to further elucidate the long term safety and efficacy of DOACs in this high risk patient population.

Limitation and Implication for Future Research

Several of the limitations in this systematic review should be considered when the findings are interpreted. Second, the included studies in heterogeneity are the patient populations, the study designs and follow up duration. Little is known regarding use of DOACs in severe CKD or end stage

renal disease (eGFR < 30 mL/min/1.73m²), and several studies were done on moderate chronic kidney disease (CKD). Patient variability and study methodology may introduce variability that limits the robustness of our conclusions in subjects for example, on dialysis, which have the most complex anticoagulant management [1].

In addition to this, the review discovered that there was a consistent decline in stroke risk as well as reduction in bleeding problems in use of DOACs but not mortality outcomes. This has implications for long term benefits of DOACs in terms of overall survival of this patient group. Since there is lack of survival advantage in most studies including those by Kato et al. (2020), Zhang et al. (2021) and many others, further investigation into long term outcomes such as cardiovascular mortality, all cause mortality is warranted [2, 5]. Thus, a gap in this need more comprehensive studies with longer follow up periods.

This review also lacks some of the included studies for bias. Most studies had high methodological quality, but small sample sizes in some may exclude the ability to detect significant differences in outcomes, including mortality and renal function. In addition, there was an implementation of the risk of the selection bias and reporting bias due to some studies using observational data rather than randomized controlled trials. The lack of randomized controlled trials in this field, noted by Smith et al. (2022), demonstrates a pressing need for well designed prospective studies to better establish more robust evidence on the use of DOACs in AF patients with CKD [6].

Limitation: variability of renal dosing strategies of DOACs between studies. However, many studies had not reported details of how the renal function was monitored or adjusted during the course of treatment, and this might affect both efficacy and safety outcome. The focus of this variability highlights the necessity of standardized DOAC dosing guidelines in CKD patients, especially in those with a renal impairment.

However, the findings of this review have some important implications for future research. The long term efficacy and safety of DOACs needs to be evaluated in further large scale, randomized controlled trials in different CKD populations including those with advanced renal disease and those with end stage renal disease and dialysis. Future studies should close current literature gaps by addressing mortality outcomes and should consider the effect of DOAC on patient centered outcomes (bleeding complications, renal function, quality of life).

In addition, there is an important need for research to define more refined dosing strategies of DOACs in the presence of variable degrees of renal impairment. The studies of pharmacokinetic modeling and renal dose adjustments for DOACs would be able to provide insights into the fine tuning of these medications to individual patient need. In addition, future research should further examine at what point in time there are effects on renal function with longer term use of DOACs, and especially in patients with advanced CKD where the risk of drug accumulation is increased.

Finally, although progress has been made in this area with DOACs, the limitations of current research emphasize that more work is required to demonstrate that they will be a safer and more effective treatment option compared to warfarin in all AF patients with CKD, and confirm or answer the open questions in certain subgroups of patients. Understanding the DOACs in this high-risk population helps us to expand our knowledge of how these drugs are utilized in this population such that we can better inform the clinical practice and anticoagulant therapy in CKD patients.

CONCLUSION

This systematic review describes the comparative efficacy and safety of direct oral anticoagulants (DOACs) versus warfarin in atrial fibrillation patients with chronic kidney disease (CKD). The findings suggest that stroke prevention and bleeding risk reduction should be improved by DOACs compared with warfarin, especially in patients with moderate CKD. There were no significant differences between the two groups in mortality outcomes, but DOACs were consistently associated with fewer bleeding complications and may provide a safer alternative to anticoagulation for AF patients with renal impairment. However careful thinking is required before prescribing DOACs to patients with severe CKD or end-stage renal disease due to the need to adjust dosing, monitor renal

function, and consider alternatives.

While promising, the current evidence base is limited by much heterogeneity in study design, small sample sizes, and a paucity of long-term follow-up, and should be scrutinized further. Large-scale randomized controlled trials to evaluate long-term outcomes of DOACs in AF patients with CKD, including effects on mortality, renal function, and quality of life, should be future studies. Furthermore, there is also a need for more precise dosing strategies and guidelines for DOACs use in advanced CKD, with a view to optimal patient care.

Finally, the results suggest that DOACs hold great promise to reduce AF patients with CKD and achieve improved outcomes, but further research is definitely needed to define the best treatment strategy for this high-risk population.

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