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Systematic Review

Impact of Renal Function on Apixaban and Rivaroxaban Use in Stroke Patients with Atrial Fibrillation

Wilhelmina N. Hauwanga [1], Abisola M. Olowofeso *[2], Amoolya R. Amaravadhi [4], Marwa Kdouk [3], Johny Davilma [5], Onyinye Ebiliekwe [3], Ifunanya R. Ekeocha [6], Abdelwahab Ahmed [7], Pranav Tiyyala [3], Hassan A. Ahmed [3], Billy McBenedict [3]

[1]Cardiology, Faculty of Medicine, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil.
[2]Public Health, University of Illinois, Springfield, USA.
[3]Neurosurgery, Fluminense Federal University, Niterói, Brazil.
[4]Internal Medicine, Malla Reddy Institute of Medical Sciences, Hyderabad, India.
[5]Internal Medicine, St Elizabeth Youngstown Hospital - Neomed, Youngstown, USA.
[6]Internal Medicine, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.
[7]Internal Medicine, Kassala University Hospital, Kassala, Sudan.

*Corresponding Author: Name: Abisola Olowofeso; *aolow@uis.edu*

Abstract

Objective: To assess how renal function influences the efficacy and safety of apixaban and rivaroxaban in patients with atrial fibrillation (AF) and chronic kidney disease (CKD). ***Design:*** Systematic review following PRISMA guidelines. ***Methods:*** A comprehensive literature search identified studies published between 2018 and 2024 evaluating apixaban or rivaroxaban use in AF patients with varying degrees of renal impairment. Twenty-six studies meeting inclusion criteria were reviewed for outcomes related to stroke prevention, bleeding risk, and dose adjustment. ***Results:*** Apixaban and rivaroxaban were both effective in stroke prevention among AF patients with CKD. However, apixaban consistently demonstrated a superior safety profile, with lower rates of major bleeding, particularly in patients with moderate to severe CKD or on dialysis. This benefit is attributed to apixaban's lower renal clearance compared with rivaroxaban, which often required dose modification in renal impairment. Most studies favored apixaban for patients with advanced CKD, while rivaroxaban use was associated with higher bleeding risk in severe renal dysfunction. ***Conclusion:*** Apixaban offers favorable safety and comparable efficacy to rivaroxaban in AF patients with CKD. Individualized anticoagulation strategies guided by renal function are essential, and further studies are warranted in end-stage renal disease populations.

Keywords: ***Atrial Fibrillation; Stroke Prevention; Chronic Kidney Disease; Renal Insufficiency; Apixaban; Rivaroxaban; Anticoagulants.***

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, contributing significantly to morbidity, increased stroke risk, and mortality [1]. AF occurs when irregular electrical signals in the atria disrupt the heart's normal rhythm, causing it to fibrillate instead of contracting efficiently. Globally, AF affects approximately 33.5 million people, with common risk factors including aging, coronary artery disease, hypertension, and heart failure [1]. Hence, anticoagulation therapy is crucial for reducing stroke risk in patients with AF. AF-related thromboembolisms, which originate from the left atrium in approximately 90% of cases, significantly contribute to stroke incidence [2]. Anticoagulants, such as heparins, vitamin K antagonists, and thrombin inhibitors, work by targeting the coagulation pathway to prevent clot formation [3]. While anticoagulation therapy has been shown to reduce AF-related stroke risk by over 60%, the risk of both new and recurrent strokes remains substantial [4]. Studies have shown a stepwise increase in AF risk with declining renal function, with those in the advanced stages of chronic kidney disease (CKD) facing up to a fourfold increase in the incidence of AF compared to individuals without CKD [5]. The complex interplay between the kidneys and cardiovascular system exacerbates conditions such as hypertension, volume overload, and systemic inflammation, which can lead to structural and electrical remodeling of the atria, further promoting the development of AF [6].

In patients with both AF and CKD, managing the dual risk of stroke and bleeding presents a clinical challenge. Renal impairment alters the pharmacokinetics of anticoagulants, making it necessary to closely monitor renal function and adjust treatments accordingly. Evidence suggests that even mild CKD increases the risk of stroke and adverse outcomes in AF patients, highlighting the importance of tailored anticoagulation strategies [6]. CKD patients also exhibit a higher incidence of AF-related complications such as heart failure and sudden cardiac death, necessitating vigilant follow-

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up and individualized therapy to mitigate these risks [5]. Thus, careful management of renal function is essential for improving outcomes in this high-risk population.

The use of oral anticoagulants, particularly non-vitamin K antagonist oral anticoagulants (NOACs) like Apixaban and Rivaroxaban, has revolutionized stroke prevention in patients with AF. These agents are preferred over traditional warfarin due to their predictable pharmacokinetics, fewer dietary interactions, and lack of routine coagulation monitoring [7]. However, the choice between Apixaban and Rivaroxaban in patients with AF is highly influenced by renal function, given that both drugs rely to varying extents on renal clearance for elimination [8].

Several studies have evaluated the impact of renal function on the efficacy and safety of Apixaban and Rivaroxaban in AF patients at risk of stroke. These studies emphasize the need for careful patient selection and the adjustment of dosing regimens based on estimated glomerular filtration rate (eGFR) to maximize therapeutic benefit while minimizing the risk of adverse outcomes [7,9]. This review aims to explore the influence of renal function on the use of Apixaban and Rivaroxaban in stroke prevention among patients with AF, highlighting the differences in efficacy, safety, and clinical outcomes between these two agents across varying levels of renal impairment.

Materials and Methods

The systematic review adhered to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the organization and reporting of its results [10]. An electronic search was conducted across several research databases, including PubMed, Embase, and Web of Science (Table 1). These databases were accessed on August 8, 2024. The search covered the period from 2018 to 2024.

Table 1: Summary of the search strategy employed for searching the databases

Database	Search strategy	Filters used
PUBMED	((Anticoagulation [Title/Abstract] OR "Anticoagulation therapy"[Title/Abstract]) AND (Stroke [Title/Abstract] OR "cerebrovascular accident*"[Title/Abstract] OR "brain vascular accident*"[Title/Abstract])) AND ("Atrial Fibrillation"[Title/Abstract]) AND ("Kidney injury"[Title/Abstract] OR "renal function"[Title/Abstract] OR "chronic kidney disease"[Title/Abstract] OR "renal disease"[Title/Abstract])	Exclude preprints, Humans, english, 2018 -2024
Embase	(anticoagulation:ab,ti OR 'anticoagulation therapy':ab,ti) AND (stroke:ab,ti OR 'cerebrovascular accident*':ab,ti OR 'brain vascular accident*':ab,ti) AND ('kidney injury':ab,ti OR 'renal function':ab,ti OR 'chronic kidney disease':ab,ti OR 'renal disease':ab,ti) AND 'atrial fibrillation':ab,ti	([article]/lim OR [article in press]/lim OR [conference paper]/lim) AND [english]/lim AND [2018-2024]/py
WEB OF SCIENCE	(anticoagulation OR 'anticoagulation therapy') AND (stroke OR 'cerebrovascular accident*' OR 'brain vascular accident*') AND ('kidney injury' OR 'renal function' OR 'chronic kidney disease' OR 'renal disease') AND 'atrial fibrillation'	2018 - 2024

Inclusion Criteria and Exclusion Criteria

For this review, studies were included if they focused on the efficacy and safety of Apixaban and Rivaroxaban in patients with AF, particularly in relation to stroke prevention and systemic embolism in patients with varying degrees of renal impairment. Research that directly compared these anticoagulants in populations with CKD, including those on dialysis, was prioritized to assess their differential impacts. Studies evaluating bleeding risks, including gastrointestinal and intracranial hemorrhage, as well as those that examined the use of reversal agents such as Andexanet alfa, were also considered relevant. Randomized controlled trials (RCTs), and observational studies published in peer-reviewed journals were included to ensure broad coverage of clinical outcomes.

Studies were excluded if they primarily focused on anticoagulants other than Apixaban and Rivaroxaban, such as Warfarin or Dabigatran, unless these anticoagulants were part of a direct comparison with Apixaban or Rivaroxaban. Research that did not report on specific outcomes related to stroke prevention, systemic embolism, or bleeding risk in AF patients with renal impairment was also excluded. Additionally, case reports, conference abstracts, and studies not published were excluded to maintain a high level of scientific rigor and ensure the inclusion of full, peer-reviewed data. Studies without sufficient detail on the patient population's renal function or those that lacked adequate safety and efficacy outcome measures were not considered. Studies not published in English were excluded.

Results

Through our search strategy, we identified a total of 552 articles (Figure 1), comprising 175 from PubMed, 143 from Embase, and 234 from Web of Science. Filters were applied based on the inclusion/exclusion criteria. The articles were transferred to an Excel sheet, where 304 duplicates were manually removed, resulting in 248 articles. These 248 articles were further scrutinized based on their titles and abstracts, leading to the disqualification of 210, leaving 38 articles. Full texts for 38 articles were retrieved for eligibility assessment. After a thorough full-text review, 9 papers were excluded, resulting in 29 articles being included in the final review (Table 2). Data screening was independently conducted by two review authors, with a third reviewer consulted in cases of disagreement. Notably, no automated tools were utilized in this process.

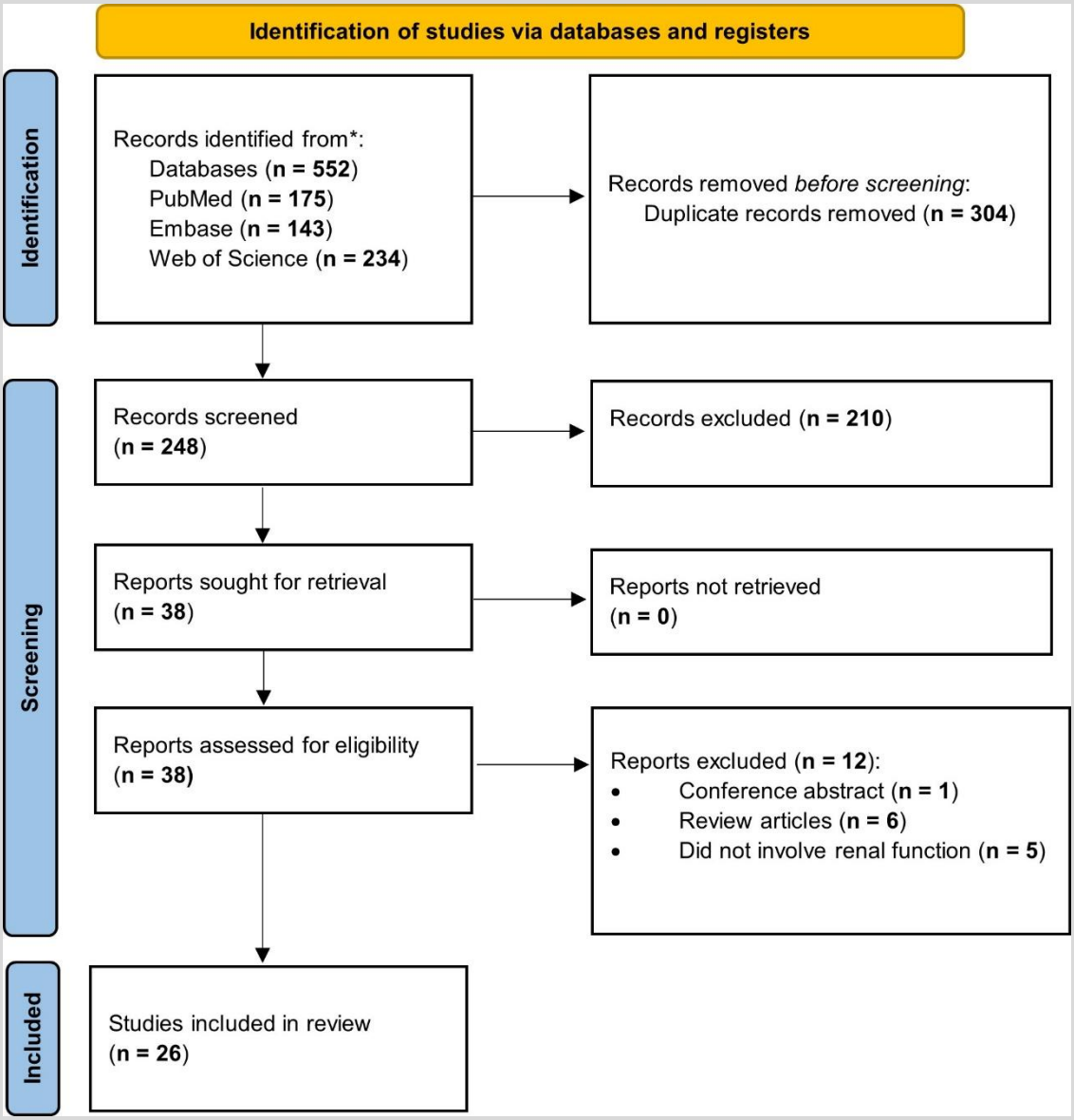

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram indicating the steps taken to filter the articles for this review

Table 2: Summary of studies included in this review, along with their respective demographics and key findings.

Author	Demographic data	Key findings
[7]	6,744 patients (41.6% female, median age 72 years). Patients with NVAF and severe kidney disease or those undergoing hemodialysis were divided into two groups (rivaroxaban = 1896, warfarin = 4848).	Rivaroxaban was associated with 32% reduction in major bleeding risk compared to Warfarin in the patients.
[8]	40,564 patients (mean age 75 years, 42.6% male) with nonvalvular AF were studied for anticoagulation outcomes.	Reduced-dose direct oral anticoagulants (DOACs) showed lower risks of major, gastrointestinal, and intracranial bleeding, and hemorrhagic stroke compared to warfarin in nonvalvular AF patients, though rivaroxaban increased major bleeding risk.
[11]	313 patients (52.35% male, median age 75 years) with moderate/severe renal impairment were studied for AF treatment outcomes	Warfarin resulted in fewer bleeding complications compared to rivaroxaban in AF patients with renal impairment, though both drugs showed similar stroke rates, highlighting the need for dosing adjustments
[12]	60 patients were identified (male= 31, female = 29)). The mean age of patients was 80.3 + 7.4 years. 20 mg Rivaroxaban was prescribed to 58.3 %, 15 mg Rivaroxaban was prescribed to 33.3%, and lower or unknown doses were prescribed to the remaining 8.3%. Higher dose than recommended based on renal function was present in 35% of patients and concurrent antiplatelet therapy occurred in 70%.	Patients experiencing rivaroxaban major bleeding in practice were elderly, often renally impaired and on concurrent antiplatelet therapy. The study highlights the need for careful management and monitoring of these patients especially during transitions of care.

[13]	18140 patients (male=11755, female=6393); Mean age: 70.0 (63.0 to 76.0). Patients with AF and at least one risk factor for stroke were placed into two groups based on discontinuance of AF therapy (permanent discontinuation = 4063, non-permanent discontinuation = 14077)	22.4% of patients discontinued the study drug early, with warfarin having a higher discontinuation rate than apixaban. Patient request (46.1%) and adverse events (34.9%) were the primary reasons.
[14]	1443 patients (52.8% female, mean age 77.2 ± 9.7 years, CHA_2DS_2-VASc = 4.1 ± 1.5). Patients were divided into four groups (rivaroxaban = 46.0%, dabigatran = 24.4%, apixaban = 22.5% and edoxaban = 7.1%)	The study found that DOACs showed a good safety and effectiveness profile in real-life clinical practice, with low rates of stroke, major bleeding, and intracranial bleeding.
[15]	patients = 56504 (male, female = 51.39%, 48.61%); origin = korean; mean age = 70.8±11.0 to 74.3±8.9. The patients with mean CHA_2DS_2-VASc score score of 2 or more (18.4% received warfarin, 81.6% were treated with NOACs)	NOACs were associated with lower risks of thromboembolic events and major bleeding compared to warfarin. NOACs showed better effectiveness and safety outcomes than warfarin, but unjustified underdosing of apixaban may reduce clinical benefits
[16]	132 patients on hemodialysis were randomized into three groups and given: VKA, Rivaroxaban, and Rivaroxaban + Vitamin K2, and followed for 18 months. Then followed up for an additional 18 months	Although VKA and DOAC (Rivaroxaban) groups had a similar risk of stroke, cardiovascular events and major bleeding complications occurred more frequently with a VKA than with a DOAC suggesting that VKAs should be avoided in patients on hemodialysis.
[17]	1762 individuals on warfarin, 71 (4.0%) switched to apixaban (57.8% male, mean age 78.2 years (SD ±6.6), 78.9% white, mean CHA2DS2VASc 5.0 (SD ±1.5), mean HAS-BLED 2.2 (SD ±0.5) and 1691 (96.0%) continued warfarin (47.6% male, mean age 80.1 years (SD ±8.7), 87.9% white, mean CHA2DS2-VASc 5.5 (SD ±1.6), mean HAS-BLED 2.5 (SD ±0.8).	The incidence of stroke and major bleeding was numerically lower in the apixaban switch group compared to the warfarin continuation group, but the differences were not statistically significant due to a small size of the apixaban group.
[18]	Patient 182; male=118(64.8%); female= 64 (35.2%); mean age 69.59	The incidence of major bleeding or CRNMB was also similar in both treatment groups. There was no difference in the mortality rate associated with the anticoagulant treatment used. there was a trend toward lower all-cause mortality in patients on apixaban compared with those on rivaroxaban.
[19]	186,405 new DOAC users over a period of 8 years. males = 46.4% -58.9%; females = 41.1% - 53.6%; Most of the patients were 75 or older (48.8% in Mondriaan to 60.8% in BIFAP). The mean age ranged from 69.3 (Mondriaan) to 75.7 (BIFAP). Patients with NVAF were categorized into three based on DOAC of interest (dabigatran =28%, rivaroxaban = 49%, apixaban = 22%)	The incidence of DOAC use increased over the study period, with apixaban and rivaroxaban usage rising while dabigatran usage decreased. There was significant variability in patient characteristics, comorbidities, and dose adjustments across different countries
[20]	Total of 49 458 patients; mean age was 72.2±10.1 years; 48 708 (98.5%) were male; Black =~13%; Other races = ~87%. Patients with Heart failure and AF were grouped into two (warfarin = 23 635; DOAC = 25 823)	DOACs, especially apixaban and dabigatran, were associated with lower bleeding and mortality rate than warfarin. However, declining renal function led to an increase in patients who were given DOACs.
[21]	Patient = 340; male = 158; female = 182 . Patients with NVAF and placed on two doses of Apixaban (5 mg or 2.5 mg) were separated into two groups based on renal function (preserved renal function pRF = 287, mean age 73.71 ± 9.99; impaired renal function iRF = 53, mean age 74.23 ± 11.24).	None of the patients on an apixaban regimen higher than approved labeling (n=13) experienced a bleeding event. Of those patients treated with an apixaban regimen lower than approved dosage (n=48), four (8.83%) experienced a major bleed and five (10.4%) experienced a minor bleed. Numerically, there were similar major bleeding events in the pRF group compared to the iRF group (4.41 vs. 3.57%, P=0.66) with similar results with apixaban 2.5 mg (10 vs. 16%, P=0.47).
[22]	patients: 1,455; male =815, female = 640, Mean age: 78.5. Patients were divided into with AF and advanced CKD two categories based on the type of therapy used, DOAC (rivaroxaban) or VKA (rivaroxaban = 764, VKA =691).	Rivaroxaban was associated with fewer adverse kidney outcomes and lower all-cause mortality compared to VKAs and may thus be a better treatment option for patients with AF and advanced CKD.
[23]	patients: 1,544; male: 862; female: 682; Mean age: 80. Patients were divided into 3 groups based on whether they received OAC therapy or not (rivaroxaban n = 764, VKA n = 691, w/oOAC n =89).	In practice, patients who received no OAC for treating AF with advanced CKD are likely to be older and have a higher risk of bleeding. This group however also received more antiplatelet drugs more frequently.
[24]	Patient: 24,974; male; female; mean age: 66	The NOACs were associated with a lower risk of ischemic stroke. In patients with CrCl >95 mL/min, NOACs had a better net clinical benefit than warfarin (HR for the composite outcome, 0.79; 95% CI, 0.65–0.96). The weighted cumulative incidence curves showed lower ICH rates in each NOAC than in warfarin.

[25]	Patient = 9578; male = 6321; female= 3257. Patients with AF and put on Rivaroxaban treatment were followed up 1 year into the treatment and separated into two groups based on history of prior ischemic stroke/TIA (with history= 2153, mean age 75.7±9.3; without history = 7425, mean age 72.4±9.8)	Patients with prior ischemic stroke/TIA experienced higher rates of bleeding and thromboembolic events compared to those without.
[26]	2492 patients; mean age = 71 ± 11 years; male = 55.7%; female = 45.3%; mean CHA2DS2-VASc score 3.7 ± 1.6, mean HAS-BLED risk scale 2.2 ± 0.9). Patients who were administered DOACs were divided into two groups based on the presence of morbid obesity (morbid obesity = 135, Non-morbid obesity = 1994).	There were no significant differences in mortality, ischemic stroke, or major bleeding rates between morbidly obese patients and the general population, suggesting that DOACs are safe for treating morbidly obese patients.
[27]	A total of 34,569 patients, 43.1% female, with a mean age of 71.2 years	A machine learning method identified patient subgroups with varying outcomes associated with oral anticoagulant use, suggesting that treatment for atrial fibrillation can be personalized to optimize outcomes
[28]	1403 patients on peritoneal dialysis (PD) (186 or 13.2% with non-valvular atrial fibrillation)	It is important for caretakers of patients on PD to be trained on AF and anticoagulation therapy since there is a high incidence of AF in these patients.
[29]	15,000 individuals, approximately 50% male, with an mean age of 65 years	The study demonstrates that large-scale application of precision medicine can improve cardiovascular outcomes by identifying novel genetic variants linked to cardiovascular diseases.
[30]	The study analyzed 24,426 patients, 51.1% female, with a median age of 76 years	found that apixaban and dabigatran were associated with higher odds of stroke compared to rivaroxaban, particularly in older and higher risk patients
[31]	154 patients (median age 68.0, (female 56, black 69)	Prematurely stopped, thus patient population lacks the size to make accurate predictions.
[32]	1204 SPAF patients (male = 631, female = 573, median age = 70 yrs) receiving rivaroxaban were followed for 6.7 ± 3.4 years with a mean rivaroxaban exposure of 4.9 ± 3.5 years.	Rivaroxaban therapy is effective and safe for long-term use in SPAF patients as rates of stroke/TIA/systemic embolism decreased over time, though bleeding patterns may change over time due to aging and co-morbidities
[33]	patients: 17,156; male: 10,586; female: 6,571; Mean age: 66.2. Dialysis patients with nonvalvular AF were categorized into three groups administered Warfarin (73%), Apixaban-at recommended dose (13.9%), Apixaban-below recommended dose (13.1%).	Both DOACs performed better than Warfarin (VKA), as apixaban was associated with lower risk of major bleeding. However, there was no difference in bleeding risk, risk of stroke or systemic embolism between Apixaban-at recommended dose, Apixaban-below FDA recommended dose. However, only Apixaban-at recommended dose significantly reduced mortality risk compared to warfarin compared to warfarin.
[34]	The study involved 98 patients with CKD, 45% male, with a median age of 67 years. The patients who had chronic kidney disease including those on dialysis were divided into three groups based on dosage of apixaban received twice daily (BID): (2.5 mg BID = 73, 5.0 mg BID = 22, and 10.0 mg BID= 3)	No significant differences were found between the 2.5 mg BID and 5.0 mg BID dosage groups in terms of major bleeding events, ischemic stroke, venous thromboembolism, or any bleeding. Further clinical trials with larger patient populations are needed to make more conclusive inferences.

AF- Atrial Fibrillation; DOACs- Direct Oral Anticoagulants; NOACs- non-vitamin K antagonist oral anticoagulants.
CHA2DS2-VASc– Congestive heart failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (metric for estimating risk of stroke in patients with AF)NVAF- non-valvular atrial fibrillation; VKA- Vitamin K Antagonists; BIFAP-Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (A Pharmacopedia data resource of Spain); HAS-BLED - Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol (metric for bleeding risk); CRNMB-clinically relevant non-major bleeding
DOACs- Direct oral anticoagulants CKD - Chronic Kidney disease OAC- Oral Anticoagulation Therapy
PD - peritoneal dialysis BID- bis in die (twice daily) SPAF- Stroke Prevention in Atrial Fibrillation

Study quality and bias assessment

The quality of the articles was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools (Table 3). The JBI appraisal tool includes questions that allow for the assessment of the quality of articles in a systematic review. In addition, it allows for the identification of biases, errors, or flaws in the study methodologies, results and/or conclusions drawn. Hence, this process also led to the removal of poor-quality articles. All studies included in the analysis focused on a clearly defined issue regarding the impact of renal function on Apixaban and Rivaroxaban use in stroke patients with AF. Studies recruited participants in a clearly defined manner or clearly stated how samples were obtained (Table 3). However, numerous studies displayed significant differences in gender representation among participants.

Table 3: The quality assessment using the JBI Critical Appraisal Tool

Checklist question	Selected publications																									
	[7]	[8]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]
Were there clear criteria for inclusion in the case series?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants included in the case series?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were valid methods used for the identification of the condition for all participants included in the case series?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the case series have the consecutive inclusion of participants?	Y	Y	Y	N/A	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	Y	N	Y	Y	N	Y	Y	Y
Did the case series have a complete inclusion of	Y	N	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

participants?																									
Was there clear reporting of the demographics of the participants in the study?	NC	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Were the outcomes or follow-up results of cases clearly reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there clear reporting of the presenting sites' or clinics' demographic information?	N/A	Y	N	NC	NC	N	N	NC	Y	N	N	N/A	N	Y	N	N	Y	NC	Y	N/A	Y	N/C	N/A	Y	N	N
Was the statistical analysis adequate?	Y	Y	Y	NC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	**7/9 (79 %)**	**8/9 (89 %)**	**8/9 (89 %)**	**6/9 (67 %)**	**6/9 (67 %)**	**7/9 (78 %)**	**8/9 (89 %)**	**6/9 (67 %)**	**8/9 (89 %)**	**7/9 (79 %)**	**8/9 (89 %)**	**7/9 (79 %)**	**7/9 (79 %)**	**9/9 (100 %)**	**8/9 (89 %)**	**8/9 (89 %)**	**8/9 (89 %)**	**7/9 (79 %)**	**9/9 (100 %)**	**7/9 (79 %)**	**9/9 (100 %)**	**8/9 (89 %)**	**7/9 (79 %)**	**8/9 (89 %)**	**7/9 (79 %)**	**8/9 (89 %)**
classification	**Mod**	**Low**	**Low**	**Mod**	**Mod**	**Mod**	**Low**	**Mod**	**Low**	**Mod**	**Low**	**Mod**	**Mod**	**Low**	**Low**	**Low**	**Low**	**Mod**	**Low**	**Mod**	**Low**	**Low**	**Mod**	**Low**	**Mod**	**Low**

Y= Yes, N= No, NC= Not clear, N/A= Not Applicable Mod = Moderate

Joanna Briggs Institute (JBI) appraisal checklist is based on nine items, and each item is assessed by scoring (yes = 1), (no = 0), and (not clear or not applicable = 0). The total score obtained for each individual study was presented as percentages and each study was categorized according to different levels of risk of bias (high risk of bias if 20–50% items scored yes, moderate risk of bias if 50–80% items scored yes, and low risk of bias if 80–100% items scored yes as per the JBI checklist.

Discussion

Efficacy of Apixaban and Rivaroxaban

1. Prevention of Stroke

The efficacy of Apixaban and Rivaroxaban in preventing stroke recurrence in patients with AF, particularly those with varying degrees of renal impairment, is a crucial consideration in clinical practice. Both apixaban and rivaroxaban have been shown to reduce the risk of stroke in patients with non-valvular atrial fibrillation (NVAF), with studies demonstrating their effectiveness across different levels of renal function. Similar ischemic stroke rates were recorded across DOACs, including Apixaban and Rivaroxaban, at 0.7 events per 100 patient-years. However, when comparing their relative efficacy, Apixaban appears to offer a slight advantage over Rivaroxaban in stroke prevention [14]. This is in agreement with the Cho *et al.*[15], study which reported a hazard ratio (HR) of 0.68 for Apixaban versus 0.74 for Rivaroxaban, indicating Apixaban's superior stroke prevention capabilities.

Studies have shown Apixaban's ability to reduce stroke recurrence in patients with NVAF and CKD, where it was shown to outperform Warfarin in reducing both hemorrhagic and ischemic strokes [8]. Similarly, both Apixaban and Rivaroxaban provided stroke prevention benefits over Warfarin, particularly in patients with a creatinine clearance (CrCl) >80 mL/min [24]. However, Apixaban maintained its stroke prevention efficacy even in more advanced stages of renal disease, while Rivaroxaban's results were mixed, particularly in patients on dialysis, where Rivaroxaban did not significantly reduce the risk of stroke recurrence [7]. This is consistent with the Albabtain *et al.*[11], study, that found comparable stroke rates between Rivaroxaban and warfarin in AF patients with renal impairment, highlighting concerns about Rivaroxaban's efficacy in this subgroup. Additionally, Kreutz and colleagues [23] noted that Rivaroxaban demonstrated non-inferiority to warfarin for patients with moderate kidney impairment but was less consistent in patients with advanced CKD. Yun *et al.* [34] also emphasized Apixaban's safety and efficacy in patients with end-stage renal disease (ESRD) on dialysis, further reinforcing its role as a safer and more effective option for stroke prevention compared to Rivaroxaban [34].

In the general population, ischemic stroke occurred at a rate of 1.9 per 100 patient-years, whereas in morbidly obese patients, the stroke rate was notably lower, at 0.8 per 100 patient-years ($p = 0.261$), despite the physiological differences in this population [26]. These findings suggest that, even though morbidly obese patients tend to have lower plasma concentrations of anticoagulant drugs, the efficacy of stroke prevention remains relatively unaffected [26]. Apixaban, often prescribed at a reduced dose of 2.5 mg every 12 hours, has emerged as a common choice for anticoagulation in patients with ESRD due to its relatively lower dependence on renal clearance compared to other anticoagulants [28,29]. The hazard ratio (HR) for Apixaban 5 mg in reducing the composite outcome of stroke and systemic embolism was 0.76 (95% CI: 0.65-0.88), reflecting a 24% risk reduction compared to warfarin, while rivaroxaban, at both 15 mg and 20 mg doses, showed similar effectiveness with HRs of 0.84 (95% CI: 0.60-1.18) and 0.83 (95% CI: 0.61-1.13), respectively [29]. In contrast, a study found that patients treated with Apixaban or Dabigatran had a significantly higher incidence of stroke than those on Rivaroxaban, with stroke odds being 1.38 times higher with Apixaban (95% CI: 1.25-1.53) and 1.26 times higher with Dabigatran (95% CI: 1.13-1.40) [30]. Despite this, both Apixaban and Rivaroxaban offer similar stroke prevention benefits when appropriately dosed, including in patients with moderate renal impairment [16].

For patients with CrCl between 30 and 49 mL/min, Rivaroxaban demonstrated non-inferiority to Warfarin in stroke prevention. In addition, Apixaban was also associated with a significantly lower risk of stroke compared to warfarin in large registries of patients with AF and renal impairment [22]. Both drugs have shown efficacy in long-term stroke prevention in AF patients, with rivaroxaban showing stroke/transient ischemic attack (TIA) rates of 3.5 per 100 patient-years in the first year, decreasing to 1.6 in years 2-5, and 2.1 beyond 5 years [32]. In patients with advanced CKD, no significant difference was observed between Apixaban and Rivaroxaban in stroke prevention [22].

2. Systemic Embolism Prevention

In terms of systemic embolism prevention, Apixaban continues to show a favorable profile compared to Rivaroxaban. Lower rates of systemic embolism were recorded in patients treated with Apixaban compared to Warfarin, with better outcomes in terms of both stroke and embolic event prevention [8]. This is further reinforced by studies demonstrating that Apixaban, Rivaroxaban, and Dabigatran show lower systemic embolism rates compared to warfarin, with Apixaban reporting an incidence rate of 2.82 per 100 person-years, slightly outperforming Rivaroxaban's 2.83 per 100 person-years [15]. Both drugs contribute to a comprehensive strategy against stroke and embolism, although Apixaban tends to be favored in patients with compromised renal function. For patients with CrCl >95 mL/min, Apixaban has shown the lowest rates of thromboembolic events, making it particularly effective in preventing both stroke and systemic embolism [14,24]. In contrast, Rivaroxaban did not significantly reduce systemic embolism rates compared to warfarin, particularly in patients with severe renal impairment or those on dialysis [7]. Apixaban's more favorable pharmacokinetic profile, with lower renal clearance, makes it a potentially safer option for preventing systemic embolism in patients with renal dysfunction [21].

No cases of systemic embolism were reported in the morbidly obese group treated with either Apixaban or Rivaroxaban, demonstrating their effectiveness in preventing embolic events [26]. In the general population, the rate of systemic embolism was similarly low at 0.2 per 100 patient-years ($p = 0.652$), underscoring the efficacy of these anticoagulants across different body weights and renal functions [26]. Both DOACs, Apixaban and Rivaroxaban, offer a favorable alternative to Vitamin K antagonists (VKAs), consistently showing significant reductions in embolic events, particularly when adjusted for renal function [16]. Apixaban demonstrates a reduction in systemic embolism with fewer renal-related adverse events and long-term data supports the continued efficacy of both drugs in preventing systemic embolism, contributing significantly to the reduction of thromboembolic complications [23,32]. Comparative studies indicate no substantial difference between Apixaban and Rivaroxaban in systemic embolism prevention, although both outperform Warfarin in patients with moderate CKD [23,31,33].

Safety Profiles of Apixaban and Rivaroxaban

1. Bleeding Risks and Renal Impairment

Bleeding risk is a significant concern when choosing between Apixaban and Rivaroxaban, particularly in patients with renal impairment. Apixaban has a well-documented safety profile, with a lower risk of major bleeding, including gastrointestinal and intracranial hemorrhage. Apixaban is associated with significantly

fewer major bleeding events compared to both Warfarin and Rivaroxaban. Specifically, gastrointestinal bleeding was notably lower in patients treated with Apixaban [8]. This safety advantage can be partially attributed to Apixaban's lower reliance on renal clearance, which helps reduce the risk of drug accumulation and bleeding in patients with impaired kidney function. In contrast, Rivaroxaban has been linked to a higher risk of bleeding, particularly in patients with impaired renal function. Coleman *et al.*[7] reported a 32% reduction in major bleeding compared to warfarin, but Rivaroxaban still carried a higher overall bleeding risk, especially gastrointestinal bleeding, in patients with CKD. Similarly, Albabtain *et al.*[11] found that Rivaroxaban led to more frequent major bleeding events in patients on dialysis. Wetmore *et al.*[33] also supported these findings, noting that Apixaban, whether dosed according to or below the label, was associated with a significantly lower risk of major bleeding compared to warfarin, particularly in patients undergoing dialysis [33].

Renal impairment plays a crucial role in influencing the bleeding risks of both Apixaban and Rivaroxaban due to their differing degrees of renal clearance. Apixaban, with approximately 27% renal clearance, is better suited for patients with advanced CKD. Its safer profile in this population is well-documented, as highlighted by Jansson *et al.*[8], where Apixaban's lower reliance on renal excretion minimized the risk of drug accumulation and subsequent bleeding. Rivaroxaban, on the other hand, has a higher reliance on renal clearance, with approximately 66% of the drug excreted via the kidneys. This makes it a riskier option for patients with renal impairment, especially those with end-stage renal disease or on dialysis, as drug accumulation can increase the likelihood of bleeding. Coleman *et al.* emphasized the importance of careful dose adjustments in these patients to mitigate this risk [7].

Renal function plays a crucial role in determining the safety and efficacy of anticoagulants like Apixaban and Rivaroxaban, particularly in patients with CKD. Apixaban, with a lower renal clearance of 25%, has demonstrated a safer profile in patients with CKD stage 4-5 compared to warfarin, which is not cleared by the kidneys [17]. Apixaban consistently shows a lower risk of major bleeding compared to Rivaroxaban, particularly in patients with impaired renal function [27]. This difference is significant in elderly patients and those with moderate to severe renal impairment (eGFR <60 mL/min), where Apixaban's safety profile remains superior [28]. Rivaroxaban, while effective, presents a higher risk of gastrointestinal bleeding, especially in patients with CrCl <30 mL/min, where 35% of patients received higher-than-recommended doses, exacerbating bleeding risks [12]. Both Apixaban and Rivaroxaban show better safety profiles compared to Warfarin, but Apixaban, with its lower renal clearance of 27% compared to Rivaroxaban's 35%, is preferred in patients with renal impairment due to its lower overall bleeding risk [30]. Major bleeding rates for Rivaroxaban are higher during the first year of use but decrease over time, although renal impairment remains a significant risk factor [32].

In patients with CKD, Apixaban is often favored due to its lower rates of life-threatening bleeding episodes, particularly in those with severe renal dysfunction, while Rivaroxaban presents a better safety profile compared to Vitamin K antagonists (VKAs) but remains riskier than Apixaban [16]. The overall safety profile of these drugs highlights the importance of renal function monitoring and dose adjustment to minimize bleeding risks, especially in patients with advanced CKD.

2. Reversal Agents and Bleeding Management

The development of specific reversal agents has significantly improved the safety profile of these non-vitamin K oral anticoagulants (NOACs) by providing a mechanism to rapidly reverse their anticoagulation effects in emergency situations. Andexanet alfa, a recombinant modified human factor Xa (FXa) decoy protein, acts as a reversal agent for both Apixaban and Rivaroxaban. It works by binding to these direct FXa inhibitors, thereby neutralizing their anticoagulant effects. This reversal agent is particularly valuable in situations of uncontrolled or life-threatening bleeding, such as gastrointestinal or intracranial hemorrhages, where rapid reversal of anticoagulation is necessary [11].

The availability of Andexanet alfa has certainly improved the safety profiles of both Apixaban and Rivaroxaban in real-world practice, but its use should be carefully balanced against the patient's renal profile to minimize risks. This is particularly crucial in managing bleeding complications, where dose adjustments and careful monitoring of renal function play a significant role [15,34]. Additionally, studies have shown that prothrombin complex concentrates (PCCs) can be used alongside Andexanet alfa to manage critical bleeding events, though Apixaban's shorter half-life and more predictable pharmacokinetics may provide an added safety margin, especially in CKD patients [22,27].

Although warfarin has a well-established history of bleeding management protocols, including the use of vitamin K, recent advancements have provided similar options for DOACs like Apixaban and Rivaroxaban. These agents, particularly Apixaban, are noted for their lower reliance on renal function, which reduces the complexity of managing bleeding in patients with renal impairment [20]. However, reversal agents like Andexanet alfa are now considered essential in managing life-threatening bleeds, with clinical outcomes showing success rates of 75-85% in mitigating critical bleeding events [13].

Both Apixaban and Rivaroxaban have established reversal strategies using Andexanet alfa, a specific reversal agent for factor Xa inhibitors, to manage life-threatening bleeding events [18]. In practice, both Apixaban and Rivaroxaban demonstrate comparable safety profiles to warfarin, with the use of Andexanet alfa and prothrombin complex concentrates providing critical support in managing severe bleeding [29]. Although specific data on reversal agent usage were limited, studies consistently referenced their importance in mitigating bleeding risks during emergencies [12,30].

For patients with compromised renal function, the availability of these agents enhances the clinical management of bleeding, given the prolonged clearance of these anticoagulants in such populations [16]. The use of these agents is supported in practice, with monitoring of renal function and appropriate dose adjustments being key strategies to prevent adverse bleeding events [11]. Apixaban, with its shorter half-life and renal excretion profile, offers an added safety margin, making bleeding management less complex [22]. Meanwhile, in Rivaroxaban users, andexanet alfa and agents like activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa are critical tools for bleeding management, ensuring safety across varied patient groups, including those at higher risk due to renal impairment [32].

Impact of Renal Function on Therapy

Renal function plays a critical role in determining the safety and efficacy of both anticoagulants. Apixaban, with its lower dependence on renal clearance (27%), is favored in patients with mild to moderate renal impairment, as demonstrated in the ARISTOTLE trial, which reported a 15% reduction in major adverse events in these patients. Conversely, Rivaroxaban shows higher bleeding risks, particularly in those with severe renal impairment

(GFR <30 mL/min), underscoring the need for careful patient selection [13].

In patients on Apixaban, regular renal function monitoring is essential to ensure appropriate dosing, especially in those with moderate to severe CKD. Jansson *et al.*[8] emphasized that adhering to dosing guidelines based on renal function is critical in minimizing bleeding risks and maximizing the drug's efficacy. In contrast, Rivaroxaban requires more frequent monitoring and dose adjustments, particularly in patients with eGFR below 50 mL/min. Improper dosing in these patients increases bleeding risks, as highlighted by Coleman *et al.*[7], who stressed the need for regular renal function monitoring and appropriate dose modifications in high-risk populations, including those on dialysis [7]. Renal function significantly impacts both the dosing and safety of these anticoagulants. In patients with reduced renal function, particularly those with CrCl below 30 mL/min, Rivaroxaban poses a higher risk of bleeding complications compared to Apixaban, which has a more predictable pharmacokinetic profile, making it a safer option for patients with severe renal impairment [34]. Moreover, as shown in the Minematsu *et al.*[25] study, incorrect dosing of Rivaroxaban in patients with impaired renal function can lead to increased risks of bleeding due to overdosing or underdosing, further underscoring the importance of regular monitoring and dose adjustments.

Renal function is a key factor in the dosing and efficacy of both Apixaban and Rivaroxaban. In morbidly obese patients, better renal function was associated with a lower prevalence of impaired clearance, contributing to favorable outcomes [26]. In patients with CKD, careful dose adjustments are necessary to minimize thromboembolic risks and bleeding complications, particularly as there is a lack of randomized trials for patients with CrCl <30 mL/min [28]. Apixaban can be used safely in patients with severe renal impairment, including those on hemodialysis, as its pharmacokinetic profile remains stable [31]. Rivaroxaban requires more precise dose adjustments, especially in patients with CrCl between 30-49 mL/min, where 15 mg is recommended, while 20 mg is used for CrCl ≥ 50 mL/min [29]. Apixaban is generally preferred for patients with moderate to severe renal impairment due to its lower bleeding risk [30]. Monitoring renal function is critical, as improper dosing increases bleeding risks, particularly with Rivaroxaban, where 35% of patients were found to be on higher-than-recommended doses [12]. Apixaban shows a more favorable safety profile in CKD and ESRD patients, while Rivaroxaban has demonstrated significant reductions in adverse kidney outcomes and a lower likelihood of requiring kidney replacement therapy compared to Vitamin K antagonists [23]. Regular monitoring of renal function is essential to ensure safe therapy, especially as renal decline may necessitate changes in treatment [32].

Patient Selection and Risk Stratification

The CHA2DS2-VASc score for stroke risk and the HAS-BLED score for bleeding risk are essential tools in determining the appropriate anticoagulant therapy in patients with renal impairment, particularly those with AF. These scoring systems provide a structured approach to assessing both the risk of thromboembolic events and the likelihood of bleeding complications, which is crucial for individualized patient management. The CHA2DS2-VASc score incorporates key stroke risk factors, including age, sex, history of heart failure, hypertension, diabetes, and prior stroke or thromboembolism, to estimate a patient's annual risk of stroke. On the other hand, the HAS-BLED score evaluates the risk of major bleeding based on factors such as hypertension, abnormal renal or liver function, stroke history, bleeding history, labile international normalized ratio (INR), age, and concurrent use of medications like antiplatelets or nonsteroidal anti-inflammatory drugs (NSAIDs) [9].

In patients with moderate to severe CKD, the use of these tools becomes even more critical due to the increased complexity of managing anticoagulation therapy. The CHA2DS2-VASc score remains a valuable predictor of stroke risk even in patients with advanced renal impairment, as these patients are often at higher baseline risk for thromboembolic events [9]. However, the decision to initiate or continue anticoagulation must also consider the elevated bleeding risks associated with renal dysfunction, which is where the HAS-BLED score plays an important role. Coleman *et al.*[7] emphasized the need for careful balancing of stroke and bleeding risks, particularly in patients with stage 4 or 5 CKD or those on hemodialysis, where both the CHA2DS2-VASc and HAS-BLED scores should guide therapeutic decisions [7].

Studies consistently show that Apixaban provides better outcomes in patients with high CHA2DS2-VASc scores and elevated HAS-BLED scores compared to Rivaroxaban. Apixaban's lower reliance on renal clearance (approximately 27%) makes it safer in patients with moderate to severe CKD, as it leads to fewer bleeding complications, particularly gastrointestinal and intracranial hemorrhages [8]. The study by Esteve Pastor *et al.*[9] reinforced that Apixaban is associated with a lower incidence of major bleeding even in patients with elevated HAS-BLED scores, thus providing a more favorable risk-benefit ratio in comparison to Rivaroxaban. In contrast, Rivaroxaban, with its higher dependence on renal excretion (approximately 66% cleared through the kidneys), requires more cautious monitoring and dose adjustments in CKD patients, as improper dosing can lead to an increased risk of bleeding.

Tailored therapy based on comprehensive risk assessment is crucial in managing patients with AF, particularly for anticoagulant therapy [18]. For example, the mean HAS-BLED score, a measure of bleeding risk, was lower in patients receiving apixaban (2.2) compared to those on warfarin (2.5), suggesting careful selection of lower-risk patients for switching [17]. The selection of anticoagulant therapy should always involve a thorough evaluation of both thromboembolic and bleeding risks, alongside the patient's renal function, to ensure optimal outcomes [16]. Patients with a CHA2DS2-VASc score of 6 or higher benefit most from anticoagulation, while those with a HAS-BLED score of 2 or higher require close monitoring and dose adjustments [32]. The importance of dosing apixaban according to the FDA label was emphasized, as label-concordant dosing has been shown to offer a better benefit-risk profile, particularly in terms of survival. This underscores the importance of individualized treatment plans based on renal function, bleeding risks, and stroke risk stratification when selecting between apixaban and rivaroxaban [23].

Conclusion

This systematic review highlights the crucial role that renal function plays in determining the efficacy and safety of Apixaban and Rivaroxaban for stroke prevention in patients with AF. Apixaban consistently demonstrated superior safety and efficacy across varying levels of renal impairment, particularly in patients with moderate to severe CKD and those on dialysis. Its lower reliance on renal clearance makes it a preferred option for this high-risk population, offering effective stroke prevention with a reduced risk of major bleeding events compared to Rivaroxaban. Rivaroxaban, while effective in stroke prevention, showed a higher bleeding risk in patients with impaired renal function, necessitating more frequent dose adjustments based on eGFR.

Both anticoagulants provide significant benefits over traditional Vitamin K antagonists (VKAs), but Apixaban's favorable safety profile makes it the better choice in patients with renal impairment. Given the variability in patient responses to anticoagulation, individualized treatment strategies, including regular monitoring of renal function and tailored dosing, are essential to optimize outcomes. Further research is warranted to refine anticoagulation strategies, particularly in patients with end-stage renal disease, to further reduce the risks of both stroke and bleeding in this vulnerable population.

Declarations

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Conflict of Interest

The authors have no conflicts of interest to declare.

Ethics Approval

Not applicable. This study is a systematic review of previously published literature and did not involve human participants or animals.

Human Rights Statement

The authors confirm that this work aligns with the principles of the United Nations Declaration of Human Rights and the journal's statement against war and violence.

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