Journal of Pioneering Medical Sciences
Received: February 26, 2026 | Accepted: May 03, 2026 | Published: June 05, 2026
Volume 15, Issue 05, Pages 222-229
DOI https://doi.org/10.47310/jpms2026150530

Comparative Safety and Pharmacokinetic Variability of Direct Oral Anticoagulants in Patients with Chronic Kidney Disease: A Systematic Review

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Abstract: Background: Anticoagulation therapy becomes more challenging in patients with chronic kidney disease (CKD) due to the increased risk of thromboembolic and bleeding events. While DOACs have several benefits over more conventional treatments, there is still much we don't know about their pharmacokinetics and safety in CKD. **Objective:** In order to conduct a comprehensive analysis of the relative safety and pharmacokinetic variability of DOACs in CKD patients. **Methods:** In accordance with PRISMA 2020 standards, a systematic review was carried out. Up to December 2025, electronic databases were combed through. We considered studies that looked at the pharmacokinetics, bleeding risk, and thromboembolic outcomes of DOACs in CKD. Eleven research, comprising pharmacokinetic studies, randomized trials, and cohort studies, fulfilled the inclusion criteria. **Results:** Significant pharmacokinetic variability was observed across DOACs. Dabigatran showed high renal dependence and increased accumulation risk in advanced CKD, while apixaban demonstrated stable pharmacokinetics and minimal dialyzability. Rivaroxaban exhibited intermediate characteristics. In hemodialysis populations, dabigatran and rivaroxaban were related to higher rates of bleeding, but apixaban consistently linked with a decreased major bleeding risk than warfarin. Evidence regarding thromboembolic outcomes was mixed, with some studies showing no significant benefit of anticoagulation in dialysis patients. **Conclusion:** DOACs demonstrate variable safety and pharmacokinetic profiles in CKD. Apixaban appears to offer the most favorable balance between efficacy and safety, while dabigatran should be avoided in advanced CKD. Individualized treatment decisions are essential, and to determine the best anticoagulation therapies for this group, further randomized trials are required.

Key Words: Chronic Kidney Disease, Direct Oral Anticoagulants, Apixaban, Rivaroxaban, Dabigatran, Pharmacokinetics, Hemodialysis, Bleeding Risk, Thromboembolism, Anticoagulation

INTRODUCTION

A leading cause of death and disability, chronic kidney disease (CKD) worsens with time, largely driven by its strong association with cardiovascular disease and thromboembolic complications. Patients with impaired renal function frequently require anticoagulation in cases like this

atrial fibrillation and venous thromboembolism, placing them at increased risk for both thrombosis and bleeding. This coexistence of opposing risks makes anticoagulant selection particularly challenging in this population [1].

Warfarin and other vitamin K antagonists (VKAs) have long been the backbone of anticoagulant treatment for chronic kidney disease (CKD) patients. The need for regular monitoring to sustain therapeutic anticoagulation, as well as their variable pharmacokinetics and a plethora of medication and food interactions, make their usage difficult. These limitations are further exacerbated in CKD, where altered metabolism and reduced renal function contribute to increased variability in drug response and possibly unfavorable results [2].

Compared to VKAs, direct oral anticoagulants (DOACs) have better predictable pharmacokinetics, set dosage regimens, and less need for frequent laboratory testing, all of which have greatly altered anticoagulation treatment. Reasons for their broad use include the positive safety profiles shown in large-scale clinical studies and the fact that they are more convenient to use [3,4]. Despite these advantages, their use in patients with CKD remains complex due to differences in renal elimination among individual agents [5].

An essential part of renal function is the pharmacokinetics of DOACs, influencing their absorption, distribution, metabolism, and excretion. As kidney function declines, reduced drug clearance may lead to accumulation and increased bleeding risk. Conversely, inappropriate dose reduction or avoidance may compromise therapeutic efficacy, increasing the risk of thromboembolic events. This delicate balance underscores the importance of understanding drug-specific pharmacokinetic profiles in patients with renal impairment [6].

Importantly, DOACs differ significantly in their pharmacokinetic characteristics, including the extent of renal excretion and bioavailability. These differences may result in variable safety and efficacy outcomes across stages of CKD. For instance, agents with lower renal clearance may provide more stable exposure in advanced CKD, whereas those with higher renal dependence may carry increased risks of accumulation. Understanding these variations is critical for optimizing anticoagulant therapy in this vulnerable population [7].

Patients with severe chronic kidney disease (CKD) and end-stage renal disease (ESRD) have traditionally been under- or excluded-represented in randomized controlled studies assessing anticoagulant treatments, despite their increasing clinical use. As a result, available evidence remains limited and sometimes inconsistent, complicating clinical decision-making and guideline development. This evidence gap highlights the need for comprehensive evaluation of both pharmacokinetic and clinical outcomes in this population [8,9].

Bleeding complications remain a major concern when prescribing anticoagulants to patients with renal impairment, as both minor and serious bleeding episodes may have a considerable effect on death rates, hospitalization rates, and quality of life. In addition, CKD is associated with complex alterations in hemostasis, resulting in a paradoxical state characterized by both increased bleeding and thrombotic tendencies. These factors necessitate careful individualized risk–benefit assessment when selecting anticoagulant therapy [10,11].

A number of variables, including age, comorbidities, concomitant medicines, and the degree of renal failure, contribute to the pharmacokinetic heterogeneity in chronic kidney disease. While observational studies involving real-world patients with decreased renal function have shed light on the usage of DOACs, the results cannot be applied to a broader population due to research design and population heterogeneity. To better understand the pharmacokinetic variability and comparative safety profiles of DOACs in CKD, as well as to facilitate more educated and personalized clinical decision-making, a comprehensive review of the relevant literature is necessary [12-15].

METHODOS

Study Design

The researchers behind this study used a systematic review approach that adheres to the standards set forth by PRISMA 2020 to guarantee their work is transparent, rigorous, and reproducible. The major goal of this study was to collect and assess the available data about the relative safety and pharmacokinetic variability of direct oral anticoagulants (DOACs) in individuals suffering from chronic kidney disease (CKD).

Apixaban, rivaroxaban, and dabigatran are direct octave angiotensin-converting enzyme (DOAC) medications that have been the subject of recent research on their pharmacokinetic profiles, bleeding risk, thromboembolic outcomes, and dosage considerations in patients with different degrees of renal impairment, including those with end-stage renal disease (ESRD) who need hemodialysis. To fully comprehend medication behavior and safety in this high-risk group, pharmacological and clinical data were both taken into account.

Eligibility Criteria

Predetermined inclusion and exclusion criteria were used to select the studies:

Inclusion Criteria

- **Population:** All patients identified as having chronic kidney disease, such as patients with severe CKD or end-stage renal disease (ESRD) who are receiving hemodialysis, must be adults (≥18 years old).
- **Interventions/Exposures:** Take apixaban, rivaroxaban, dabigatran, or edoxaban, which are all direct oral anticoagulants (DOACs).
- **Comparators:** Warfarin, other DOACs, or no anticoagulation therapy.
- **Outcomes:** Pharmacokinetic parameters (e.g., area under the curve, half-life, drug clearance), bleeding

events (large-scale and mild bleeding), thromboembolic incidents (stroke, systemic embolism), and death rates.
- **Study Designs:** Randomized controlled trials, cohort studies (either planned or retrospective), and pharmacokinetic/pharmacodynamic investigations.
- **Language:** Publications only in the English language.
- **Publication Period:** Research released from 2010 to 2025 to illustrate current DOAC use.

Exclusion Criteria

- Non-empirical studies (e.g., reviews, editorials, commentaries)
- Research concerning pediatric cohorts
- Studies lacking CKD-specific subgroup analysis
- Conference abstracts excluding full-text access
- Redundant publications or intersecting datasets

Eleven papers fulfilled all qualifying criteria and were included into the final synthesis.

Search Strategy

From the beginning of the database up to December 2025, a thorough literature search was carried out throughout many electronic databases, such as PubMed, Scopus, Web of Science, Embase, and Google Scholar. Boolean operators and various keyword combinations were employed in the search strategy:

- ("chronic kidney disease" OR "CKD" OR "end-stage renal disease" OR "ESRD" OR "hemodialysis")
- AND ("direct oral anticoagulants" OR "DOACs" OR "apixaban" OR"rivaroxaban" OR "dabigatran" OR "edoxaban")
- AND ("pharmacokinetics" OR "drug clearance" OR "half-life")
- AND ("bleeding" OR "safety" OR "thromboembolism" OR "stroke")

For further comprehensiveness, we manually checked the reference lists of all the included research and related review articles. We loaded all the collected information into our reference management program and deleted any duplicates before screening.

Study Selection Process

Two separate reviewers were responsible for selecting the studies. A first step was determining the relevancy of titles and abstracts. After that, the evaluation of full-text publications was done using the previously established criteria for inclusion and exclusion.

Reviewers discussed and ultimately reached a consensus on matters of disagreement. When two reviewers could not reach a consensus, a third reviewer was asked to weigh in. Using a PRISMA flow diagram (Figure 1), which shows the steps of identification, screening, eligibility, and inclusion, the whole selection process is described.

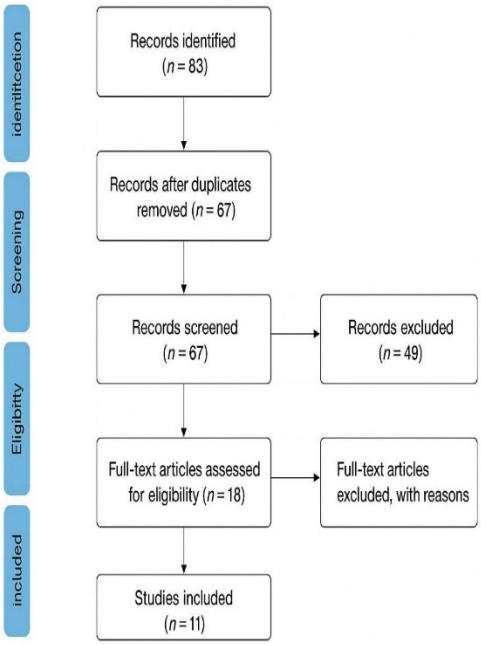

Figure 1 PRISMA Flow Diagram

Data Extraction

Prior to its implementation, a standardized data extraction form underwent pilot testing. From all of the studies that were considered, the following data was retrieved:

- Author(s), publication year, and country
- Study design and setting
- Sample size and patient characteristics (e.g., CKD stage, dialysis status)
- Type and dose of DOAC used
- Comparator treatment (e.g., warfarin or other DOACs)
- Pharmacokinetic parameters (e.g., area under the curve, half-life, drug removal by dialysis)
- Clinical outcomes, including bleeding events, thromboembolic events, and mortality
- Key findings and conclusions

Data extraction was performed independently by two reviewers, with cross-checking to ensure accuracy and completeness.

Quality Assessment

A variety of standardized evaluation measures tailored to each study's unique design were used to determine the included studies' methodological quality:

- **Newcastle–Ottawa Scale (NOS):** for observational cohort studies.
- **Cochrane Risk of Bias tool (RoB 2):** for randomized controlled trials.
- **Pharmacokinetic study appraisal criteria:** focusing on sample size, methodology, and reporting of PK parameters.

We checked each research for selection bias, group comparability, outcome assessment, and clear reporting. Researchers graded the quality of the studies using a scale from poor to high.

Limitations in observational design, limited sample numbers in pharmacokinetic investigations, and possible confounding variables led to most research being graded as mediocre quality.

Data Synthesis

A narrative synthesis method was used since there was a lot of variation in the research designs, demographics, and outcome measures. Important theme areas were used to arrange the findings:

- Pharmacokinetic variability of DOACs across CKD stages
- Evaluations of comparative safety, with a focus on the danger of hemorrhage
- Thromboembolic outcomes and efficacy
- Comparisons between DOACs and vitamin K antagonists
- Dosing considerations in renal impairment

Quantitative results (e.g., hazard ratios, relative risks, pharmacokinetic measures) were reported descriptively. Discordance in outcome definitions, research designs, and assessment methodologies necessitated avoiding a meta-analysis.

Ethical Considerations

There was no need for ethics clearance or informed consent since this research relied on already available data. It is presumed that all included studies had the necessary ethical permissions in place before data collection and that they were all peer-reviewed. Research integrity, openness, and accurate reporting were maintained throughout the evaluation process in compliance with PRISMA 2020 requirements.

RESULTS

Direct Oral Anticoagulants and Their Comparative Safety and Pharmacokinetic Variability in Chronic Kidney Disease Patients: A Systematic Review Reviewing and Interpreting Included Studies

Study Designs and Populations: The eleven papers that were included exhibited a range of methodological methods to assessing direct oral anticoagulants (DOACs) in patients with chronic kidney disease (CKD). These studies comprised pharmacokinetic (PK) investigations, retrospective cohort studies, and one randomized controlled trial (RCT). Pharmacokinetic investigations (e.g., Khadzhynov *et al.* [16], De Vriese *et al.* [17], and Mavrakanas et al. [18] provide detailed insights into drug disposition, while large observational studies (e.g., Chan *et al.* [19] and Siontis *et al.* [20] offer real-world safety and effectiveness data.

From little pharmacokinetic studies (n = 12–18) to massive administrative cohorts (n = more than 25,000 patients), sample sizes vary greatly. Patients with severe chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD) and hemodialysis (HD), were the primary focus of most investigations. The length of the follow-up varied, ranging from short-term observational follow-up of less than five years to longer-term pharmacokinetic evaluations of a single dosage.

Pharmacokinetic Variability Across CKD Stages

Substantial pharmacokinetic variability was observed across DOACs, primarily driven by differences in renal elimination.

Dabigatran demonstrated the greatest dependence on renal clearance. In the study by Khadzhynov *et al.* [16], Approximately 48.8% to 59.3% of the medication in circulation was eliminated after a single 4-hour hemodialysis session, and there was very little redistribution of the drug after dialysis (<16%). The expected pharmacodynamic effects were confirmed by the linear connection between anticoagulant activity and plasma medication concentrations. However, the high reliance on renal excretion explains the significant risk of drug accumulation in advanced CKD.

With a half-life of around 8.6 hours and no appreciable buildup after repeated dosage, hemodialysis was shown to be ineffective in removing rivaroxaban, as shown by De Vriese *et al.* [17]. Substantial drug exposure was achieved with a 10 mg dosage in HD patients, which is equivalent to a 20 mg dose in healthy persons. In terms of pharmacokinetic stability, apixaban was the clear winner. In patients with maintained renal function, a lower dosage of 2.5 mg twice daily produced drug exposure equivalent to regular dosing, according to Mavrakanas *et al.* [18]. In contrast, the usual dose of 5 mg twice daily led to supratherapeutic levels. The amount of apixaban that was eliminated by dialysis was only around 4%.

Comparative Safety Outcomes: Bleeding Events

Several studies evaluated bleeding risk among DOACs and compared them with warfarin. Chan *et al.* [19] reported that dabigatran was associated with a 48% increased risk of bleeding compared with warfarin (RR 1.48), while rivaroxaban increased risk by 38% (RR 1.38), raising concerns about their safety in hemodialysis populations.

The opposite is true according to the results of Siontis *et al.* [20], who discovered that apixaban considerably reduced the incidence of serious bleeding when compared to warfarin (HR 0.72). Also, as compared to warfarin and reduced-dose apixaban, the risks of stroke, systemic embolism, and death were lower with standard-dose apixaban (5 mg twice daily).

Apixaban users had a lower rate of serious bleeding events (0 vs. 7 occurrences) compared to warfarin users,

according to Sarratt *et al.* [21], however this difference wasn't statistically significant. Also, in patients with severe CKD, Stanifer *et al.* [22] showed that apixaban reduced the risk of significant bleeding by 66%.

Comparative Safety Outcomes: DOAC-to-DOAC Comparisons

Miao *et al.* [23] analyzed rivaroxaban and apixaban in end-stage renal disease (ESRD) patients undergoing hemodialysis and found no statistically significant variations in the risk of stroke, systemic embolism, or serious bleeding. These findings suggest comparable safety and efficacy between the two agents, although statistical power may have been limited.

Thromboembolic Outcomes and Efficacy

When compared to warfarin, Siontis *et al.* found that standard-dose apixaban decreased the risk of systemic embolism and stroke.

However, Mavrakanas *et al.* [24] found insignificant reduction in stroke risk with apixaban compared with no anticoagulation, but observed an increased risk of fatal or intracranial bleeding (HR 2.74), highlighting the complexity of anticoagulation decisions in ESRD patients.

Comparison with Vitamin K Antagonists

Yang *et al.* [25] reported suboptimal anticoagulation control among CKD patients receiving warfarin, with poor time in therapeutic range (TTR).

The FAERC study [10] treated patients with DOACs had a lower risk of cerebrovascular events compared to those treated with acenocoumarol, but there was no statistically significant difference in the outcomes of bleeding or death.

Randomized Trial Evidence

In hemodialysis patients, the VALKYRIE study compared rivaroxaban with vitamin K antagonists [26]. Although there were no significant differences in the course of vascular calcification, the trial did show that groups treated with rivaroxaban had fewer serious bleeding episodes.

Dosing Considerations

In order to attain the desired drug exposure in hemodialysis patients, pharmacokinetic findings suggest reducing the dosage of apixaban from 2.5 mg twice day. However, clinical outcomes data suggest that standard dosing may provide better outcomes in patients who do not meet formal dose-reduction criteria.

This discrepancy highlights the complex relationship between pharmacokinetics and clinical outcomes and underscores the importance of individualized dosing strategies.

Overall Interpretation

From what we can tell from the trials apixaban has the best safety profile of the DOACs used to treat CKD. It has a lower risk of bleeding and is just as effective as, or perhaps more effective than, warfarin. The reason for this is probably because of its steady pharmacokinetics and reduced renal clearance.

Dabigatran, due to its high renal elimination, is associated with increased bleeding risk and is generally not recommended in advanced CKD. Rivaroxaban shows mixed evidence, with pharmacokinetic stability but inconsistent safety outcomes across studies.

Overall, DOAC use in CKD requires careful patient selection, dose adjustment, and individualized risk–benefit assessment, particularly in patients with ESRD.

Table 1: Features and Main Outcomes of the Included Studies

Study	Country	Design	Sample Size	Population	Intervention	Follow- up	Key Results
Khadzhynov *et al.* [16]	Germany	Phase I PK	ESRD patients	HD patients	Dabigatran	Single dose	48.8–59.3% removed by HD; minimal redistribution
Chan *et al.* [19]	USA	Retrospetive cohort	29,977	AF + HD	Dabigatran, rivaroxaban vs warfarin	Variable	Dabigatran RR 1.48; rivaroxaban RR 1.38 bleeding risk
De Vriese *et al.* [17]	Belgiu m	PK/PD	18	HD patients	Rivaroxaban 10 mg	Single/multiple	Not dialyzable; no accumulat ion
Mavrak anas *et al.* [18]	USA	PK	12	HD patients	Apixaban 2.5 vs 5 mg	Steady state	2.5 mg therapeutic; 5 mg supratherapeutic
Sarratt *et al.* [21]	USA	Retrospective	160	HD patients	Apixaban vs warfarin	12 months	0 vs 7 major bleeds
Yang *et al.* [25]	USA	Retrospective	Multiple	AF+CKD	Warfarin	Variable	Poor TTR control
Siontis *et al.*, [20]	USA	Retrospective	25,523	AF+ESRD	Apixaban vs warfarin	Variable	↓ bleeding (HR 0.72); ↓ stroke and death
Miao *et al.* [23]	USA	Retrospective	2,623	ESRD+AF	Rivaroxaban vs apixaban	Variable	No difference in outcomes
De Vriese *et al.* [26]	Europe	RCT	132	AF+HD	VKA vs rivaroxaban	18 months	Fewer major Bleeds with rivaroxaba n
Mavrak anas *et al.* [24]	USA	Retrospective	2,082	AF+HD	Apixaban vs warfarin	Variable	No stroke benefit; ↑ bleeding
Stanifer *et al.* [22]	Multicenter	Post-hoc RCT	269	CKD (CrCl 25–30)	Apixaban vs warfarin	Trial duration	HR 0.34 for major bleeding

DISCUSSION

Patients with chronic kidney disease (CKD) may benefit since it synthesises all the existing information on the safety and pharmacokinetic variability of direct oral anticoagulants (DOACs). The results show that there is a lot of variation in how drugs work and how patients feel when they're in various stages of kidney disease, which is why this high-risk group needs tailored anticoagulation plans [15], Tham *et al.* [6]. The review highlights the importance of renal function in determining the distinct pharmacokinetic profiles of DOACs. Dabigatran, characterized by high renal clearance, demonstrated significant accumulation risk in patients with advanced CKD, consistent with prior analyses linking renal impairment to increased drug exposure and bleeding risk [9], Khadzhynov *et al.* [16]. This supports recommendations to avoid dabigatran in severe renal dysfunction.

In contrast, apixaban exhibited more stable pharmacokinetic behavior across CKD stages, likely due to its lower dependence on renal elimination. Pharmacokinetic studies demonstrated that reduced dosing in hemodialysis patients achieved drug exposure comparable to standard dosing in individuals with normal renal function [18]. However, clinical outcomes data suggested that standard dosing may provide superior protection against thromboembolic events in selected patients [20,22].

Rivaroxaban demonstrated intermediate pharmacokinetic characteristics, with limited dialyzability and altered but relatively stable exposure in hemodialysis patients [17]. These findings align with broader literature suggesting that while rivaroxaban can be used with dose adjustment, its safety profile may be less favorable compared to apixaban in advanced CKD [27].

Anticoagulants vary significantly in their risk according to the comparative safety study. According to a study conducted by Chan *et al.* in 2015 [19], hemodialysis patients were found to have an increased risk of bleeding when using dabigatran and rivaroxaban compared to warfarin. On the other hand, apixaban has shown a constant decreased risk of significant bleeding, which supports its good safety profile in populations with chronic kidney disease [20,13].

Previous studies in larger populations have shown that DOACs are just as safe as warfarin, and in some cases even better, in terms of bleeding outcomes [3] (based on observational data and randomized trials).
[4]. However, the applicability of these findings to CKD populations remains limited due to underrepresentation in clinical trials.

The balance between thromboembolic prevention and bleeding risk remains particularly complex in CKD patients. While DOACs offer effective stroke prevention, some evidence suggests that anticoagulation may not significantly reduce thromboembolic events in hemodialysis patients, while still increasing bleeding risk [25]. This underscores the need for careful patient selection. Comparative studies between DOACs have yielded mixed results. While some analyses demonstrated no significant differences between rivaroxaban and apixaban in terms of safety and efficacy [23], other studies suggest a consistent advantage for apixaban, particularly in advanced CKD [1,12] Warfarin remains widely used in CKD despite its limitations. Poor anticoagulation control and variability in therapeutic range are common in this population, contributing to increased risks of both thromboembolic and bleeding events [25]. Additionally, concerns regarding vascular calcification further limit its long-term use [8]
.

The FAERC study provided additional real-world evidence suggesting that DOACs may offer comparable or superior efficacy to vitamin K antagonists, with no significant differences in bleeding outcomes [10]. These findings support the growing shift toward DOAC use in CKD populations.
Pharmacokinetic variability remains a central factor influencing clinical outcomes. Factors such as age, comorbidities, and drug interactions contribute to interindividual variability, complicating dosing strategies and increasing the risk of adverse events [14].

Recent meta-analyses further support the safety and efficacy of DOACs in CKD, although variability in study designs and patient populations limits the strength of conclusions [5,7]. This highlights the need for more robust, CKD-specific clinical trials.

Importantly, this review highlights the disconnect between pharmacokinetic predictions and clinical outcomes. While reduced dosing may achieve target drug exposure, clinical evidence suggests that inappropriate dose reduction may compromise efficacy, particularly with apixaban [20].

Overall, the findings emphasize that DOAC selection in CKD should be guided by both pharmacokinetic considerations and clinical outcome data. While dabigatran is often to be avoided CKD, apixaban seems to provide the best balance between safety and effectiveness. With the right dosage modification, rivaroxaban may be taken carefully.

CONCLUSION

This systematic review demonstrates that direct oral anticoagulants exhibit significant variability in pharmacokinetic behavior and clinical safety across different stages of chronic kidney disease. Apixaban has the best safety profile of with less bleeding risk and the same or better effectiveness as warfarin. On the other hand, rivaroxaban has intermediate features that need careful dosage modification, while dabigatran's high renal clearance and accumulation risk provide significant safety concerns in advanced CKD.

The findings highlight the importance of individualized anticoagulation strategies that consider renal function, patient characteristics, and drug-specific properties. Evidence gaps persist, especially in patients with the benefits of DOACs over standard vitamin K antagonists. Optimal dosage regimens and better therapeutic results in this complicated group can only be achieved by future large-scale randomized studies.

Limitations

A number of restrictions apply to this. It was not possible to do a quantitative meta-analysis because, first, the included studies showed a great deal of variation in research designs, patient demographics, and outcome measures. Secondly, a lot of research relied on observational methods, which might include biases including selection bias and residual confounding. Third, pharmacokinetic studies included small sample sizes, reducing generalizability. Additionally, patients with advanced CKD and ESRD remain underrepresented in randomized controlled trials, limiting the strength of evidence. Finally, variability in dosing regimens and definitions of outcomes across studies may have influenced the interpretation of results.

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