Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease

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Prof. Sandip Mitra supervised Kathrine Parker undertaking this work.

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Review by other professional organisations
The British Society of Haematology Thrombosis taskforce have provided feedback on this guideline. The British Cardiovascular Society have consulted on this guideline.

UK Kidney Association

Contents

Executive Summary

Vitamin K antagonists have been used for the prophylaxis of thromboembolic events from atrial fibrillation for at least 40 years. Following results from large randomised controlled trials the focus has shifted to more use of direct oral anticoagulants (DOACs). DOACs have been shown to have lower rates of major bleeding with similar rates of stroke and systemic embolism (SSE) alongside simpler dosing and monitoring regimes. However, trials of DOACs excluded patients with advanced kidney disease (CrCl<30ml/min) therefore good-quality data are limited in this population making decisions around anticoagulation difficult.

In those with advanced kidney disease, especially those on dialysis, there are limited data on efficacy of anticoagulants despite an increase in bleeding risk. There are still studies ongoing to determine efficacy of anticoagulants in reducing the risk of thromboembolic stroke and systemic embolism.

The aim of these UK Kidney Association guidelines is to provide best-practice guidance on the use of anticoagulants in the context of advanced CKD. Specifically, we aim to:

- Provide guidance on use of anticoagulants in people with advanced CKD and non-valvular atrial fibrillation, focusing on the safety and efficacy
- Support the safe use of anticoagulants in clinical practice with appropriate monitoring
- Support shared decision making with people with kidney disease

We offer evidence-based graded practice guidelines covering anticoagulant use in those with CKD stage 4, stage 5 (non-dialysis) and dialysis, accompanied by recommendations for clinical research and audit. We also summarise current licensing of different anticoagulants with respect to advanced kidney disease and describe relevant parts of other national and international guideline recommendations.

This document is structured into individual modular sections to facilitate efficient revisions as the evidence base expands.

We are enormously grateful to all the members of the Guideline Working Group for their time and effort developing this guideline and to the experts who participated in the Delphi consensus supporting the recommendations made in this guideline.

Summary of recommendations

Please note for the purposes of the guideline CKD stages have been used for simplicity. This uses lab based, eGFR ml/min/1.73m^2. However, drug dosing of LMWH and DOACs should be based on Cockcroft-Gault creatinine clearance. See section 2 for further information.

Section 2	Kidney function estimates for anticoagulant dosing	Grade
	For dosing of DOACs we recommend that Cockcroft-Gault creatinine clearance should be used	**1A**
Section 3	**The use of risk scores for stroke and bleeding assessment**	**Grade**
CKD stage 4 (eGFR 15-29 ml/min/1.73m^2)		
	CHA_2DS_2VASc may be useful in assessing the risk of stroke	**2B**
	We suggest that bleeding scores are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF, and to identify particularly high bleeding risk patients for early review and follow up	**2D**
CKD stage 5 (eGFR <15 ml/min/1.73m^2 not on dialysis) and dialysis (haemodialysis/peritoneal dialysis)		
	We suggest that stroke and bleeding risk scores are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF	**2D**
Section 4	**Treatment options for NVAF thromboprophylaxis**	**Grade**
	Anticoagulation should be considered as an option for NVAF thromboprophylaxis in patients with - CKD stage 4, CKD stage 5 and patients on dialysis	**2C**
	Not offering any anticoagulation may be considered an option, particularly in those with CKD stage 5 CKD or on dialysis	**2C**
	We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different treatment options, see appendix 1	**2C**
	For patients on the deceased- donor kidney transplant waiting list who are to be offered anticoagulation we suggest this is with a VKA	**2D**
CKD stage 4 (eGFR 15-29 ml/min/1.73m^2)		
	For NVAF thromboprophylaxis we suggest offering either: - Apixaban 2.5mg twice daily - Edoxaban 30mg daily - Rivaroxaban 15mg daily - VKA	**2B**
CKD stage 5 (eGFR<15 ml/min/1.73m^2 not on dialysis)		
	For NVAF thromboprophylaxis we suggest offering either: - Apixaban 2.5mg twice daily - VKA	**2C**
Dialysis (haemodialysis/peritoneal dialysis)		

	For NVAF thromboprophylaxis we suggest offering either: - Apixaban 2.5mg twice daily - VKA	**2C**
	Patients on haemodialysis who are therapeutically anticoagulated should initially undergo dialysis without additional dialysis circuit anticoagulation	**2D**
Section 5	**Oral anticoagulant monitoring and follow up**	**Grade**
	We recommend that warfarin therapy should be monitored using the international normalised ratio (INR). Frequency of monitoring and dose adjustments should be defined in local protocols	**1A**
	We recommend that anticoagulation control with warfarin should be assessed using Time in Therapeutic range (TTR), aiming for a TTR ≥65%	**1B**
	For patients with advanced kidney disease including those on dialysis discuss options of where INR monitoring can take place and allow patient to choose if there are multiple options	**2D**
	Anticoagulation with vitamin K antagonists should be reassessed where TTR is less than 65%. This assessment should take into account adherence, cognitive function, illness, interacting medications, and lifestyle factors	**2C**
	We suggest that monitoring of peak and trough DOAC levels is not necessary in advanced CKD unless an additional reason to monitor is present i.e. potential interaction	**2C**
Section 6	**Left Atrial Appendage Occlusion**	**Grade**
	In selected patients Left Atrial Appendage may be considered	**2B**

Section 1: Background, aims and concise methods

Background

Individuals with kidney disease are at a higher risk of developing non-valvular atrial fibrillation (NVAF), the risk increasing with the severity of kidney disease. Patients with advanced kidney disease have increased rates of ischaemic stroke, independent of NVAF. In addition, there is a paucity of quality data to support anticoagulant use in reducing risk of stroke and systemic embolism, particularly in those on dialysis. Anticoagulation is also complicated by the increased risk of bleeding events in advanced kidney disease, defined for the purpose of this guideline as eGFR<30ml/min/1.73m^2. Recommendations are therefore required to support shared decision making in these patients. Due to the paucity of published data, a group of experts in the field of anticoagulation took part in a modified e-Delphi to identify statements of consensus that could provide an expert opinion of practice. The methodology for this is detailed later in this section.

This section provides a background to the guideline by discussing a) the increased risk of stroke and NVAF in advanced kidney disease and b) the increased bleeding risk in advanced kidney disease.

Introduction

Chronic kidney disease

Chronic Kidney Disease (CKD) is common and associated with a risk of progression to renal replacement therapy. In 2023, there was an estimated 3.3 million people in the UK living with CKD stages 3-5 [(1)] and this figure is expected to rise due to increasing cases of diabetes, heart disease, high blood pressure and obesity. For this guideline the term advanced CKD will refer to those with an eGFR<30ml/min/1.73m^2 which includes CKD stage 4, stage 5 (non-dialysis) and dialysis as defined by Kidney Disease Improving Global Outcomes (KDIGO)[(2)].

Atrial fibrillation in advanced CKD

Patients with CKD have an increased risk of developing NVAF, which has been reported in up to 32% of a dialysis cohort [(3)]. A systematic review showed declining renal function as an independent risk factor for stroke in patients with NVAF on oral vitamin K antagonists, relative risk (RR) 2.2 [95% Confidence interval 1.85–2.66] [(4)]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) an international, observational study of haemodialysis (HD) practices and outcomes in countries with large populations of dialysis patients found 12.5% of prevalent haemodialysis patients had AF. Within this study Japan had the lowest at 5% and Belgium the highest rates at 18% [(5)]. A systematic review from 2012 identified the prevalence of AF was 11.6% in dialysis patients and the overall incidence was 2.7/100 patient-years [(6)], however these figures are likely to have increased given an aging and increasingly co-morbid population.

The Stockholm CREAtinine Measurements (SCREAM) Project followed up non-dialysis, non-transplant adults with eGFR<60ml/min/1.73m^2 over a mean of 3.9 years [(7)]. They identified that 12% developed AF, with the incidence being higher in those with lower eGFR. Atrial fibrillation was associated with an increased risk of death and stroke after adjustment [(7)].

In a Danish cohort of AF patients, Olesen et al, found there was an increased risk of stroke and systemic embolism for those with non-end stage renal impairment and end-stage renal disease compared to those with no renal impairment [(8)].

There appears to be a bi-directional relationship with NVAF and CKD, where not only does the risk of NVAF increase with CKD but NVAF causes renal function decline. This was shown in a large propensity-matched study from Taiwan where during 10-year follow up NVAF was associated with a significantly increased risk of eGFR decline compared to those without NVAF [9]. This is postulated to be related to the kidneys' predisposition to embolic events, due to high blood flow, with obstruction of the renal microvasculature by small emboli. This may not lead to any clinical symptoms. Recurrent silent infarction of the kidney could then result in the continuous decline of renal function in patients with AF, especially those with pre-existing CKD [9].

Ischaemic stroke and systemic embolism in advanced CKD

Stroke is associated with significant morbidity and mortality causing approximately 40,000 deaths in the UK each year. Ischaemic stroke accounts for 85% of all strokes, caused by arterial occlusion. Risk factors for stroke include lifestyle factors such as smoking, established cardiovascular disease with NVAF causing up to 20% of strokes, and other medical conditions [10].

CKD is associated with an increased risk of stroke and systemic embolism (SSE). The risk of SSE increases as renal function declines with data from the US based Renal Data System reporting that CKD stage 3, stage 4, stage 5 and dialysis increased the risk of stroke by a factor 3-, 4,1-, 5.4- and 7.1-fold respectively, compared with the general population [11].

Patients on dialysis have the highest risk of stroke and after age, gender and race adjustments, hospitalization rates for ischemic stroke were found to be markedly elevated, relative risk (RR) = 4.3 to 10.1 [12]. A study examining risk factors for stroke in patients on dialysis found that prior stroke, diabetes and age at dialysis initiation were risks [6]. NVAF has not been found to increase the risk of stroke in haemodialysis patients [13,14,15], but the risk of mortality from stroke is higher, with 18% mortality in 7 days and 56% within 12 months [15]. A Canadian study found that in CKD stroke risk was increased 2-fold in those with NVAF, except for those with eGFR<30ml/min/1.73m^2 where the risk of stroke associated with NVAF had a less marked increase with Hazard Ratio (HR) 1.38 (95% CI: 0.99-1.92) [16]. Stroke risk is highest around the 30-day period prior to and after initiating dialysis with a 3-fold increased risk [3] suggesting specific dialysis factors may play a role.

In summary, stroke risk in advanced CKD is elevated compared to those without CKD, being particularly high in those on dialysis. It is unclear the extent the additional risk of NVAF has on stroke in patients with advanced CKD and it may be lower than seen in the general population.

Pathophysiology of thromboembolic risk

The in-depth pathophysiology is beyond the scope of this article but a brief overview of factors that may dispose to the prothrombotic state in co-existing AF and CKD are detailed below.

Virchow's triad describes the three main factors that contribute to thrombosis and includes endothelial injury, hypercoagulability and stasis of blood flow, of which all of these factors can be implicated [17].

The hypercoagulability in advanced kidney disease includes activation of procoagulants, decreased production of endogenous anticoagulants, platelet dysfunction, platelet activation and aggregation, and decreased fibrinolytic activity.

Key roles of the endothelium in haemostasis include the secretion of factors that modulate the coagulation cascade (for example, plasminogen activator inhibitor (PAI1) and von Willebrand factor (VWF)), vascular tone and inflammatory responses. In advanced kidney disease, inflammation-induced vascular endothelial injury or dysfunctional endothelium can promote a procoagulant state resulting from increased circulating levels of tissue factor(TF) [18], plasminogen activator inhibitor 1 (PAI-1), fibrinogen and VWF[19]. TF can lead to coagulation activation as well as being an inflammatory mediator[20]. PAI-1 also inhibits activation of the fibrinolytic system, required to break down blood clots, by inhibiting tissue plasminogen activator and urokinase. Activation of RAAS has been associated with increased plasma fibrinogen, D-dimer, and PAI-1 concentrations in hypertensive patients[21]. Platelet hyperactivity and endothelial dysfunction have been shown to be caused by uremic toxins from the gut in CKD[22]. In uraemic patients, platelets contain increased levels of P-selectin and the fibrinogen receptor PAC-1 resulting in platelet/leucocyte aggregates, as well as their increased reactivity[23].

CKD is associated with extensive myocardial fibrosis, calcification and thickening of the medial arterial layer that results in increased vascular stiffness leading to high pressure in the brain, kidney and heart further aggravating microvascular damage [23, 24]. Further, increased left ventricular afterload and reduced coronary perfusion leads to ventricular hypertrophy, ischaemia and dilation of the left atrium and ventricle leads further impairing AF related blood flow abnormalities [24].

In dialysis there are further factors that may affect development of AF which can commonly occur during dialysis sessions [25]. These include swings in fluid and electrolytes with associated neurohormonal activation and cardiac remodelling, chronic inflammation and oxidative stress alongside chronic disturbances of bone mineral metabolism, leading to valvular and vascular calcification [26, 27, 28].

Bleeding risk in advanced CKD

Patients with advanced kidney disease are at an increased risk of bleeding compared to those with normal renal function. A study from the Netherlands identified that patients with CKD had a 1.5-fold (95% CI 1.2–1.9) increased risk of bleeding, defined as fatal bleeding or bleeding requiring hospitalisation, compared to those without CKD after adjustment for factors such as age, sex, co-morbidities, antiplatelet and anticoagulant use[29]. From the Dialysis Outcomes and Practice Patterns (DOPPS) I-IV, the finding was that one in seven older patients with end-stage kidney disease, will experience a major bleeding event within 3 years of dialysis initiation[30].

The risk of bleeding is higher in those on HD compared to those on peritoneal dialysis (PD) which was shown in a prospective study from the Netherlands including 1211 HD and 534 PD patients. The authors found a 1.5-fold increased risk of bleeding for HD patients compared with PD patients when adjusted for co-morbidities and use of antiplatelets or anticoagulants[31]. This is postulated to be related to recurrent and prolonged exposure of blood to the artificial surface of the dialyser membrane and blood tubing which may induce chronic activation of platelets, leading to platelet exhaustion and dysfunction[32].

The risk of intracerebral haemorrhage (ICH) is increased in those with CKD[33]. Evidence from two large studies, the Rotterdam study and Japanese CIRCS (Circulatory Risk in Communities Study) found that in those with an eGFR<60 ml/min/1.73m^2 there was a 4-fold and 7-fold increased risk of haemorrhagic stroke in men and women, respectively[34, 35]. A further Japanese study found that for

those on dialysis the relative risk was >10-fold higher[36]. There is also an increased rate in mortality associated with an ICH in those with advanced CKD, one-year mortality with an adjusted HR of 3.02(1.91, 4.77) for those with CKD stage 4 and 4.54(2.95, 6.98) for those with CKD stage 5 and on dialysis[37].

The risk of upper gastrointestinal bleeding (UGIB) increases as renal function declines which was highlighted in a study by Liang et al who showed the increased risk across CKD stages 3-5 (not on dialysis)[38]. A Taiwanese database study identified that CKD and dialysis were independent risk factors for peptic ulcer bleeding (PUB) with a Cox proportional hazard regression analysis conferring hazard ratios (HR) of 3.99 (95 % CI 2.24-7.13) for CKD, HR 3.71 (95 % CI 2.00-6.87) for PD and HR 11.96 (95 % CI 7.04-20.31) for HD[39]. An American national Inpatient Sample identified that the OR for UGIB hospitalisation in CKD and ESKD was 1.30 (95% CI 1.17–1.46) and 1.84 (95% CI 1.61–2.09), respectively. In these groups the risk of UGIB lead to an increased risk of all-cause mortality with OR 1.47 (95% CI 1.21–1.78) and 3.02 (95% CI 2.23–4.1), for CKD and ESKD respectively. Supporting this Kuo et al identified that gastrointestinal bleeding is associated with an increased risk of mortality increased in CKD stages 3-5 not on dialysis when adjusted for other factors. There is an increase in angiodysplasias in patients with CKD compared to those without (13% versus 1.3%) and this risk was heightened in those on dialysis and with a longer duration of CKD[40]. Angiodysplasias have also been shown to be the leading cause of recurrent lower gastrointestinal (LGI) bleeding in ESKD patients, accounting for 19–32% of LGI bleeds compared with 5-6% of LGI bleeds in the general population[41].

Contributory factors for bleeding

The pathophysiology of the increased risk of haemorrhagic events is multifactorial. Factors include a direct result of uraemia-related platelet dysfunction or impaired platelet adhesion and aggregation; impaired platelet glycoprotein IIb or IIIa receptor activation; altered von Willebrand factor and nitric oxide metabolism along with anaemia[21, 24, 42]. Anticoagulant and antiplatelet use in this population may further increase the bleeding risk.

Studies indicated that uremic toxin accumulation–induced platelet dysfunction was the main cause of bleeding in patients with ESKD[43]. Uremic toxins prevent the binding of GPIIb/IIIa to fibrinogen without affecting the number of GPIIb/IIIa receptors on the platelet membrane, resulting in decreased platelet–platelet adhesion[44]. Uraemic toxins degrade the GPIb receptor on the platelet membrane, which affects the binding of VWFs with GPIb leading to reduced platelet–vessel wall adhesion[45]. Uremic toxins also induce nitric oxide and prostacyclin production in endothelial cells, causing platelet dysfunction[46]. Erythrocytes are important in moving platelets toward the vascular wall so anaemia can also contribute to the increased risk of bleeding because platelets become combined with erythrocytes and this reduces platelet vessel wall interaction[21, 24].

Licensed doses of anticoagulants for AF

Table 1. UK licensed doses of DOACs for NVAF

DOAC	Dosing		Information on renal function from manufacturer license
	CrCl 30-49 ml/min	**CrCl 15-29 ml/min**	
Apixaban	5mg BD Reduce to 2.5mg BD if TWO of: • Serum creatinine >133micromol/L • Age >80years • Weight<60kg	2.5mg BD	• Not recommended if CrCl <15ml/min
Dabigatran	110mg to 150mg BD Based on an individual assessment of the thromboembolic risk and the risk of bleeding	Contraindicated	
Edoxaban	30mg OD	30mg OD	• Not recommended if CrCl<15ml/min
Rivaroxaban	15mg OD	15mg OD	• Use with caution if CrCl 15-29ml/min • Not recommended if CrCl <15ml/min

References

1. UK KR. Kidney disease: A UK public health emergency The health economics of kidney disease to 2033 https://www.kidneyresearchuk.org/2023/06/05/kidney-disease-is-a-public-health-emergency-that-threatens-to-overwhelm-the-nhs-major-new-report-reveals/: Kidney Research Uk; 2023 [
2. Group KDIGOKCW. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2024;105(4).
3. Winkelmayer, W.C., Lui, J., Patrick, A.R., Setogu-chi, S. & Choudhry, N.K. Prevalence of atrial fibrillation and warfarin use in olderpatients receiving hemodialysis. Journal of Nephrology. 2012; 21, 341–353.
4. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GYH. Risk of Stroke or Systemic Embolism in Atrial Fibrillation Patients Treated With Warfarin. Stroke. 2013;44(5):1329-36.
5. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney International. 2010;77(12):1098-106.
6. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrology Dialysis Transplantation. 2012;27(10):3816-22.

7. Carrero JJ, Trevisan M, Sood MM, Bárány P, Xu H, Evans M, et al. Incident Atrial Fibrillation and the Risk of Stroke in Adults with Chronic Kidney Disease: The Stockholm CREAtinine Measurements (SCREAM) Project. Clin J Am Soc Nephrol. 2018;13(9):1314-20.
8. Olesen JB, Lip GYH, Kamper A-L, Hommel K, Kober L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. The New England journal of medicine. 2012;367(7):625-35.
9. Chen T-H, Chu Y-C, Ou S-M, Tarng D-C. Associations of atrial fibrillation with renal function decline in patients with chronic kidney disease. Heart. 2022;108(6):438-44.
10. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of Thromboembolism in Atrial Fibrillation: I. Clinical Features of Patients at Risk. Ann Intern Med.1992;116:1-5.
11. Bethesda. US Renal Data System, USRDS 2009 Annual Data Report Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2009.
12. Seliger, SL. et al. Elevated risk of stroke among patients with end-stage renal disease, Kidney International, Volume 64, Issue 2, 603 - 609.
13. Findlay MD, Thomson PC, Fulton RL, Solbu MD, Jardine AG, Patel RK, et al. Risk Factors of Ischemic Stroke and Subsequent Outcome in Patients Receiving Hemodialysis. Stroke. 2015;46(9):2477-81.
14. Wiesholzer M, Harm F, Tomasec G, Barbieri G, Putz D, Balcke P. Incidence of stroke among chronic hemodialysis patients with nonrheumatic atrial fibrillation. Am J Nephrol. 2001;21(1):35-9.
15. Mace-Brickman T, Eddeen AB, Carrero J-J, et al. The Risk of Stroke and Stroke Type in Patients With Atrial Fibrillation and Chronic Kidney Disease. Canadian Journal of Kidney Health and Disease. 2019;6. doi:10.1177/2054358119892372
16. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. J Am Soc Nephrol. 2013;24(7):1166-73.
17. Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. Heart. 2020 Oct;106(19):1463-1468.
18. Cetin O, Bekpinar S, Unlucerci Y, Turkmen A, Bayram C, Ulutin T. Hyperhomocysteinemia in chronic renal failure patients: relation to tissue factor and platelet aggregation. Clin Nephrol. 2006;65(2):97-102.
19. Huang MJ, Wei RB, Wang Y, Su TY, Di P, Li QP, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. BMJ Open. 2017;7(5):e014294.
20. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010;36(1):34-40.
21. Sechi LA, Novello M, Colussi G, Di Fabio A, Chiuch A, Nadalini E, et al. Relationship of Plasma Renin With a Prothrombotic State in Hypertension: Relevance for Organ Damage. American Journal of Hypertension. 2008;21(12):1347-53.
22. Fryc J, Naumnik B. Thrombolome and Its Emerging Role in Chronic Kidney Diseases. Toxins (Basel). 2021;13(3).
23. Lutz J, Menke J, Sollinger D, Schinzel H, Thürmel K. Haemostasis in chronic kidney disease. Nephrol Dial Transplant. 2014;29(1):29-40.
24. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nat Rev Nephrol. 2018;14(5):337-51.
25. Buiten, M.S., de Bie, M.K., Rotmans, J.I., Gabre€els,B.A., van Dorp, W., Wolterbeek, R., Trines,S.A., Schalij, M.J., Jukema, J.W., Rabelink, T.J.& van Erven, L. (2014) The dialysis procedureas a trigger for atrial fibrillation: new insights inthe development of atrial fibrillation in dialysispatients. Heart, 100, 685–690.

26. Goldstein, B.A., Acre, C.M., Hlatky, M.A., Tura-khia, M., Setoguchi, S. & Winkelmayer, W.C.(2012) Trends in the incidence of atrial fibrilla-tion in older patients initiating dialysis in theunited states. Circulation, 126, 2293–2301.
27. McIntyre, C.W. (2008) Calcium balance duringhemodialysis. Seminars in Dialysis, 21, 38–42.
28. Korantzopoulos, P., Kolettis, T.M., Galaris, D. &Goudevenos, J.A. (2007) The role of oxidativestress in the pathogenesis and perpetuation ofatrial fibrillation. International Journal of Cardi-ology, 115, 135–143
29. Ocak G, Rookmaaker MB, Algra A, de Borst GJ, Doevendans PA, Kappelle LJ, et al. Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study. J Thromb Haemost. 2018;16(1):65-73.
30. Sood MM, Larkina M, Thumma JR, Tentori F, Gillespie BW, Fukuhara S, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013;84(3):600-8.
31. van Eck van der Sluijs A, Abrahams AC, Rookmaaker MB, Verhaar MC, Bos WJW, Blankestijn PJ, et al. Bleeding risk of haemodialysis and peritoneal dialysis patients. Nephrology Dialysis Transplantation. 2020;36(1):170-5.
32. Toke AB. GI bleeding risk in patients undergoing dialysis. Gastrointestinal Endoscopy. 2010;71(1):50-2.
33. Vanent KN, Leasure AC, Acosta JN, Kuohn LR, Woo D, Murthy SB, et al. Association of Chronic Kidney Disease With Risk of Intracerebral Hemorrhage. JAMA Neurology. 2022;79(9):911-8.
34. Bos MJ, Koudstaal PJ, Hofman A, Breteler MMB. Decreased Glomerular Filtration Rate Is a Risk Factor for Hemorrhagic But Not for Ischemic Stroke. Stroke. 2007;38(12):3127-32.
35. Shimizu Y, Maeda K, Imano H, Ohira T, Kitamura A, Kiyama M, et al. Chronic Kidney Disease and Drinking Status in Relation to Risks of Stroke and Its Subtypes. Stroke. 2011;42(9):2531-7.
36. Iseki K, Kinjo K, Kimura Y, Osawa A, Fukiyama K. Evidence for high risk of cerebral hemorrhage in chronic dialysis patients. Kidney Int. 1993;44(5):1086-90.
37. Wang IK, Yen T-H, Tsai C-H, Sun Y, Chang W-L, Chen P-L, et al. Renal function is associated with one-month and one-year mortality in patients with intracerebral hemorrhage. PLOS ONE. 2023;18(1):e0269096.
38. Liang C-C, Wang S-M, Kuo H-L, Chang C-T, Liu J-H, Lin H-H, et al. Upper Gastrointestinal Bleeding in Patients with CKD. Clinical Journal of the American Society of Nephrology. 2014;9(8):1354-9.
39. Huang KW, Leu HB, Luo JC, Chan WL, Hou MC, Lin HC, et al. Different peptic ulcer bleeding risk in chronic kidney disease and end-stage renal disease patients receiving different dialysis. Dig Dis Sci. 2014;59(4):807-13.
40. Chalasani N, Cotsonis G, Wilcox CM. Upper gastrointestinal bleeding in patients with chronic renal failure: role of vascular ectasia. Am J Gastroenterol. 1996;91(11):2329-32.
41. Foutch PG. Angiodysplasia of the gastrointestinal tract. Am J Gastroenterol. 1993;88(6):807-18.
42. Galbusera M, Remuzzi G, Boccardo P. Treatment of Bleeding in Dialysis Patients. Seminars in Dialysis. 2009;22(3):279-86.
43. Qiu Z, Pang X, Xiang Q, Cui Y. The Crosstalk between Nephropathy and Coagulation Disorder: Pathogenesis, Treatment, and Dilemmas. J Am Soc Nephrol. 2023;34(11):1793-811.
44. Benigni A, Boccardo P, Galbusera M, Monteagudo J, De Marco L, Remuzzi G, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. Am J Kidney Dis. 1993;22(5):668-76.
45. Sloand EM, Sloand JA, Prodouz K, Klein HG, Yu MW, Arvath LH, et al. Reduction of platelet glycoprotein Ib in uraemia. British Journal of Haematology. 1991;77(3):375-81.

46. Remuzzi G, Cavenaghi AE, Mecca G, Donati MB, de Gaetano G. Prostacyclin-like activity and bleeding in renal failure. Lancet. 1977;2(8050):1195-7.

Aims

Our overriding aim is to provide practical best-practice clinical guidelines to facilitate safe and effective use of anticoagulants in the context of advanced CKD in adults. In assessing the evidence base, we have used the limited evidence and undertaken a Delphi consensus of experts in the field of nephrology, haematology and cardiology to provide best-practice recommendations. More specifically, we aimed to:

- Provide guidance on use of anticoagulants in people with CKD, focusing on the safety and efficacy; and
- Provide appropriate monitoring recommendations in people with CKD.

In order to support both use and implementation, we provide three types of recommendations:

- Use (consideration for offering anticoagulation)
- Research (what are areas of ongoing clinical uncertainty)
- Audit (can you demonstrate effective implementation)

Concise methods

Evidence synthesis by systematic review

Evidence sources and search terms

The systematic search protocol has been published in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, registration number CRD42020219449). This was published (https://link.springer.com/article/10.1007/s40620-022-01413-x) and the search was re-run to provide an update. Additional searches were added to cover the scope of this guideline, these are available in Appendix 2. The review process for this guideline was in accordance with the PRISMA statement. Several databases were searched (including EMBASE, Ovid MEDLINE and CINAHL) to obtain articles that met eligibility for the literature review. Articles included were those with a publication date from database inception to 1st March 2024 published in the English language. Full details of the PICO search tools, with all included databases and search strategies, are available in Appendix 2.

Study selection

All articles identified from the search were allocated to a predefined topic group by lead authors KP and AP. Within each topic group, abstracts were screened by two authors to determine eligibility. Articles articles were then screened by two authors to determine inclusion in the review. Any discrepancies in whether an article met inclusion criteria were dealt with by mutual agreement between the authors allocated to that topic group. Authors for each topic group are listed in Appendix 4.

Data extraction and quality appraisal

These data are summarised in the Evidence Tables (Appendix 3) and findings were used to support the rationale for the recommendations of this guideline. The recommendations and supporting rationale were reviewed by all authors and by key stakeholders prior to publication of the guidelines.

Evidence grading

We followed the principles set out in the UK Kidney Association's "Clinical Practice Guideline Development Manual" and grade evidence according to a two-tier grading system (see Table 2). We use the term "recommend" within the guideline text where Recommendations are based on Grade 1 evidence, and the term "suggest" for those based on Grade 2 evidence. We also made ungraded 'Research recommendations', which help define ongoing areas of clinical uncertainty, and we offer 'Audit measures', to define how to demonstrate effective implementation of recommendations.

Table 2: UK Kidney Association's grading system for recommendations' strength and evidence quality

Level of evidence	Evidence quality
• Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all, patients (i.e. "recommendations"). • Grade 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (i.e. "suggestions").	• Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials, or overwhelming evidence of some other sort. • Grade B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength. • Grade C evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations. • Grade D evidence is based only on case studies or expert opinion.

Generation of recommendations

From these published literature and search results, subgroups of the Guideline Working Group developed summaries of the evidence and proposed evidence-based recommendations to a joint consensus meeting of all members. All members therefore had the opportunity to review all the proposed guidelines before publication.

To develop expert opinion a Delphi was undertaken. A modified e-Delphi was undertaken with purposive sampling of experts in the field of anticoagulation including nephrology, haematology and cardiology experts listed above. Experts were identified based on their interest and had published in the field of anticoagulation in CKD. The e-Delphi involved three rounds. The first round included statements of anticoagulant use in advanced CKD, developed from the literature following a systematic review by KP, JT and AP. Experts ranked these statements on a 1-9 Likert scale where 1 was completely disagree and 9 was completely agree. For agreement on a statement the median had to fall within 7-9 and disagreement within 1-3. For a statement to achieve consensus the interquartile range (IQR) had to be within a three-point range. Statements with consensus agreement had a median of 7-9 with an IQR<3 and are included in the guideline as a practice recommendation. In round two the experts re-ranked the statements in the presence of their

previous score and the group median to try and achieve consensus in all statements. Consensus was achieved with the majority of statements. For round three it was decided to have an MS Teams meeting with discussion and anonymous voting to try and obtain consensus on the four statements that did not reach consensus.

Section 2: Kidney function estimates for anticoagulant dosing

The Medicines and Healthcare products Regulatory Agency (MHRA) published guidance highlighting the importance of using the Cockcroft-Gault (C-G) to estimate creatinine clearance for medications such as DOACs [1, 2]. The Specialist Pharmacy Service (SPS) guidance [3] suggests applying tools such as MDCALC C-G creatinine clearance calculator to allow estimation of CrCl, specifically in high-risk medications such as anticoagulation [4]. Kidney Disease: Improving Global Outcomes (KDIGO) recommend that drug dosages should be adjusted according to FDA- or EMA-approved product labelling [5]. The Delphi consensus panel of UK experts agreed that C-G creatinine clearance is important in the dosing of DOACs. For vitamin K antagonists (VKAs) consensus was that eGFR using the most recent NICE recommended formulae is appropriate.

The landmark trials in the development of DOACs used C-G to establish dose adjustments [6-9]. A review of current literature investigating methods of estimating renal function for DOACs, VKA's, and heparins demonstrated limited evidence. A selection of studies has demonstrated numerical differences or poor concordance in the estimation of renal function when different formulae are applied in the context of anticoagulation [10-19], A retrospective analysis found a combination of over and underestimation of renal function when comparing C-G to CKD-EPI, this often varied and was dependant on factors such as age, sex and weight [17]. Baseline characteristics of these subgroups were not studied and no adjustment for confounding factors were made hence these data are of limited value given the large confidence intervals and small numbers [17]. A large-scale cross-sectional study of over 70 000 people demonstrated significant variability in estimation of kidney function, especially for the older population [21]. This study compared use of eGFR and C-G using actual body weight (ABW) and ideal body weight (IBW) for estimation of renal function and was correlated to potential medicines dose changes, which included DOACs. This study was influential in recommendations made by the MHRA [1, 2]. Studies have attempted to clinically correlate the disparity in dosing due to different formulae. Yao et al identified that in over 8000 patients (2000 with CKD) there was an increase in dosing misclassification in the patients with CKD when eGFR was used and not C-G CrCl. Patients not receiving the appropriate dose had a higher risk of the clinical outcomes including SSE and major bleeding and they highlight that the use of C-G CrCl is important when dosing DOACs [19].

A national survey of prescribing practice in the UK demonstrated the need for standardisation when using formulae for estimating renal function for anticoagulant drug dosing with significant variability between health care professionals [21]. It is important to recognise that using serum creatinine to estimate kidney function has substantial limitations as concentrations are affected by muscle mass, diet, hydration, and medications and are not accurate in acute kidney injury (AKI) [3] this should therefore be taken into consideration when applying C-G.

In obesity what weight to use when calculating C-G for drug dosing is a common scenario and it is acknowledged that there is wide variation in clinical practice. A study evaluating the impact of bodyweight on C-G CrCl compared to measured 24-hour CrCl in 3678 patients found that in obesity using adjusted bodyweight (ABW) 0.4 was the most accurate way of calculating creatinine clearance [22]. This study is used by the MDCALC C-G calculator [4]. General consensus from an NHS England roundtable discussion was that ABW 0.4 would be preferred when calculating C-G for DOACs. However, there was no consensus at what point ABW should be used.

After review of the literature, evidence supports the use of C-G when estimating renal function for dosing of DOACs. This was also agreed by the Delphi consensus. Further studies are required to support alternative methods in estimating renal function due to lack of evidence on which formulae leads to the most accurate and clinically effective dosing of anticoagulants and this should be correlated to clinical outcomes.

Practice recommendations

For dosing of DOACs, we recommend that Cockcroft-Gault creatinine clearance should be used. **1A**

Research recommendations

- Use of most recent NICE recommended renal function estimating formulae for dosing of DOACs and correlation to clinical outcomes.
- In obesity what weight should be used for the C-G CrCl when calculating appropriate dose of anticoagulants.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Direct-acting oral anticoagulants (DOACs): paediatric formulations; reminder of dose adjustments in patients with renal impairment. https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-paediatric-formulations-reminder-of-dose-adjustments-in-patients-with-renal-impairment. Accessed 12 June 2024
2. Medicines and Healthcare products Regulatory Agency (MHRA). Prescribing medicines in renal impairment: using the appropriate estimate of renal function to avoid the risk of adverse drug reactions. https://www.gov.uk/drug-safety-update/prescribing-medicines-in-renal-impairment-using-the-appropriate-estimate-of-renal-function-to-avoid-the-risk-of-adverse-drug-reactions. Accessed 12 June 2024
3. Specialist Pharmacy Service (SPS). Calculating kidney function https://www.sps.nhs.uk/articles/calculating-kidney-function/. Accessed 12 June 2024
4. MDcalc. Creatinine Clearance (Cockcroft-GaultEquation). https://www.mdcalc.com/calc/43/creatinine-clearance-cockcroft-gault-equation. Accessed 12 June 2024
5. Matzke GR, Aronoff GR, Atkinson AJ, Bennett WM, Decker BS, Eckardt KU, Golper T, Grabe DW, Kasiske B, Keller F, Kielstein JT, Mehta R, Mueller BA, Pasko DA, Schaefer F, Sica DA, Inker LA, Umans JG, Murray P. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from kidney disease: improving global outcomes (KDIGO). *Kidney Int*. 2011;80:1122–37.
6. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A et al: Apixaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine,* 2011. 365(11):981-992.
7. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J et al: Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*. 2013 369(22):2093-2104.

8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP et al: Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *New England Journal of Medicine*. 2011. 365(10):883-891.
9. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al.. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *New England Journal of Medicine*. 2009; 361:1139–51.
10. Al-Maqbali JS, Al Alawi AM, Al Adawi M, Al-Falahi Z, Al-Azizi A, Al Badi K, et al.. The Clinical Associations With The Differences in Rivaroxaban Dosing in Patients with Atrial Fibrillation Stratified by three Renal Function Formulae. *Pharmacy Practice* 2023 ;21:01–6.
11. Andrade, JG, Hawkins, NM, Fordyce, CB, Deyell, MW, Er, L, Djurdjev, O, Macle, L, Virani, SA. & Levin, A. Variability in Non-Vitamin K Antagonist Oral Anticoagulants Dose Adjustment in Atrial Fibrillation Patients With Renal Dysfunction: The Influence of Renal Function Estimation Formulae'. *Can J Cardiol*, 2018 34(8). pp 1010-1018.
12. Bhalodia NJ, White EM, Achanta A, Cheng J, Deri CR, Stahl K, et al.. DOAC Dosing Discordance Using Different Estimates of Kidney Function and Outcomes. *The Journal of Clinical Pharmacology* 2023; 63:1061–6.
13. Calsolaro V, Okoye C, Rogani S, Calabrese AM, Dell'Agnello U, Antognoli R, et al.. Different glomerular filtration rate estimating formula for prescribing DOACs in oldest patients: appropriate dosage and bleeding risk. Post hoc analysis of a prospective cohort. *Aging Clinical and Experimental Research* 2022; 34:591–8.
14. Kucey M, Bolt J, Albers L, Bell A, Iroh N, Toppings J. Prescribing of Direct Oral Anticoagulants in Atrial Fibrillation Based on Estimation of Renal Function Using Standard and Modified Cockcroft–Gault Equations: A Retrospective Analysis*. Canadian Journal of Hospital Pharmacy* 2016;69.
15. Dinsa H, Nedi T, Berha AB. Concordance between modification of diet in renal disease, chronic kidney disease epidemiology collaboration and Cockcroft-Gault equations in patients with chronic kidney disease at St. Paul's hospital millennium medical college, Addis Ababa, Ethiopia. *BMC Nephrology* 2017;18. doi:10.1186/s12882-017-0783-3.
16. Melloni C, Peterson ED, Chen AY, Szczech LA, Newby LK, Harrington RA, Gibler WB, Ohman EM, Spinler SA, Roe MT et al: Cockcroft-Gault Versus Modification of Diet in Renal Disease: Importance of Glomerular Filtration Rate Formula for Classification of Chronic Kidney Disease in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes. *Journal of the American College of Cardiology* 2008, 51(10):991-996.
17. Rohla M, Pecen L, Cemin R, Patti G, Siller-Matula JM, Schnabel RB, et al.. Reclassification, Thromboembolic, and Major Bleeding Outcomes Using Different Estimates of Renal Function in Anticoagulated Patients With Atrial Fibrillation: Insights From the PREFER-in-AF and PREFER-in-AF Prolongation Registries. *Circulation: Cardiovascular Quality and Outcomes* 2021;14.
18. Wang CH, Rubinsky AD, Minichiello T, Shlipak MG, Price EL. Creatinine Versus Cystatin C: Differing Estimates of Renal Function in Hospitalized Veterans Receiving Anticoagulants. *Journal of General Internal Medicine* 2018;33:1299–306. doi:10.1007/s11606-018-4461-3.
19. Yao RJR, Holmes DN, Andrade JG, Levin A, Piccini JP, Fordyce CB. Variability in Nonvitamin K Oral Anticoagulant Dose Eligibility and Adjustment According to Renal Formulae and Clinical Outcomes in Patients With Atrial Fibrillation With and Without Chronic Kidney Disease: Insights From ORBIT-AF II. *Journal of the American Heart Association* 2023;12.
20. Wood S, Petty D, Glidewell L, Raynor DT. Application of prescribing recommendations in older people with reduced kidney function: a cross-sectional study in general practice. *British Journal of General Practice* 2018;68:e378–87

21. Parker K, Choudhuri S, Lewis P, Thachil J, Mitra S. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. *BMC Nephrology.* 2023;24.
22. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. Pharmacotherapy. 2012 Jul;32(7):604-12.

Section 3: The use of risk scores for stroke and bleeding assessment

Section 3a. Stroke risk scores in patients with chronic kidney disease

From the available observational evidence there are concerns regarding increased morbidity and/or mortality with little to no reduction in stroke risk in patients on dialysis with anticoagulation [1,2]. Risk scores are used to evaluate stroke risk and determine who would benefit most from anticoagulation.

Many clinical risk scores for stroke risk stratification have been published, with the CHA_2DS_2VASc score used in many guidelines globally [3, 4, 5, 6]. The latest 2024 European Society of Cardiology guidelines for the management of AF proposed the sexless CHA_2DS_2-VA score (Level of Evidence: C) "in the absence of other locally validated alternatives", as 'inclusion of gender complicates clinical practice both for healthcare professionals and patients' and 'omits individuals who identify as non-binary, transgender, or are undergoing sex hormone therapy" [7].

Many of the current published risk scores have not been well evaluated in those with more advanced CKD, although some data for the CHA_2DS_2VASc score are available [8, 9].

Current guideline recommendations

NICE recommends the use of CHA_2DS_2VASc to guide anticoagulant use in patients with non-valvular atrial fibrillation [3], but this risk score has not been extensively validated in patients with chronic kidney disease or in those on renal replacement therapy [8]. It makes no comments specific to patients with chronic kidney disease [3].

KDIGO classifies all patients with renal impairment as high risk, they recommend the use of anticoagulation for all patients with atrial fibrillation and chronic kidney disease (CKD 1-4) including those with a CHA_2DS_2VASc of 0-1, notwithstanding the fact that such patients would be rare given the associations of CKD with various comorbidities. They do not make a recommendation for patients who are on renal replacement therapy [10].

KDOQI suggests a modification to the AHA guidelines for stroke prophylaxis highlighting the increased risk of bleeding when prescribing stroke prophylaxis but does not give further specific recommendations [11].

The AHA recommends the use of anticoagulation for patients with CKD stage 3 and stage 4 but states it "might be reasonable" to offer treatment to patients with stage 5 or those on renal replacement therapy. It makes no specific recommendations regarding which risk assessment tool to use in such patients [4].

Performance of conventional scores in patients with CKD

See table 3 for published risk scores. However, the literature of their performance is conflicting regarding patients with CKD.

Roldan et al added CKD to $CHADS_2$ and CHA_2DS_2VASc in attempt to improve the performance of the scores without success [16]. Nakamura et al produced a novel risk score and compared this to the Framingham Stroke Risk Score [17]. It contained nine clinical variables; age, blood pressure, antihypertensive medication, smoking status, diabetes, coronary artery disease, atrial fibrillation, left ventricular hypertrophy and chronic kidney disease. They reported a statistically higher C-statistic of

this score, but the absolute difference was marginal [0.816 (95%CI, 0.794–0.838) vs. 0.800 (95%CI, 0.776–0.824), p = 0.01]. Using the data from the ROCKET AF and the ATRIA cohort Piccinni et al developed and validated the R_2CHADS_2 which includes creatinine clearance in the score, they found this improved performance over the CHA_2DS_2VASc and the $CHADS_2$ scores. The score was developed from the sub-population of the ROCKET-AF with creatinine clearance of 30-59mL/min [18].

Jong et al have studied the performance of the common stoke risk scores in patients with various levels of renal impairment [19]. This study used the data available from the Stockholm Creatinine measurements (SCREAM) project to retrospectively validate the following risk scores; $CHADS_2$, Modified $CHADS_2$, CHA_2DS_2VASc, ATRIA, and GARFIELD-AF. 36004 patients were included in this analysis over a median follow-up of 1.88 years, the majority of these patients (72.9%) had normal kidney function, 8625 patients had mild kidney impairment CKD stage 3 and a smaller number [1130] had advanced kidney disease eGFR < 30. The authors report calibration being independent of degree of renal impairment and the discrimination (C-statistic) degrading with advancing renal impairment, the Modified $CHADS_2$ score provided the best discrimination in mild to advanced kidney impairment [19].

Table 3. Current risk scores for stroke assessment

	CHA_2DS_2-VASc [12]	$CHADS_2$ [13]	GARFIELD-AF [14]	ATRIA [15]
Age	+1 to +2	√	√	√
Gender	√		√	√
Heart failure	√	√	√	√
Hypertension	√	√	√	√
Diabetes	√	√	√	√
Vascular disease	√		√	
Stroke/TIA	+2	+2		√
Renal dysfunction			√	√
Proteinuria				√

Performance of conventional scores in patients with end stage kidney disease on dialysis

Haemodialysis

The published literature for risks scores in patients on haemodialysis is also conflicting. $CHADS_2$ and CHA_2DS_2VASc have been reported to perform equally as well in dialysis patients in retrospective studies [20]. Chao et al retrospectively assessed the performance of both the $CHADS_2$ and CHA_2DS_2VASc in Taiwanese patients receiving renal replacement therapy [8]. In this study, 10999 patients were identified all of whom were not receiving any form of antiplatelet or anticoagulant, they report that both risk scores had modest C-statistics of 0.608 and 0.628 respectively.

De Jong et al used the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) a large prospective cohort of incident dialysis patients to compare the performance of 15 risk scores. They reported that all scores performed poorly with C-statistics ranging from 0.49 to 0.66 [21].

Peritoneal Dialysis

As with haemodialysis the published literature is conflicting for the performance of risk scores for patients with Atrial Fibrillation in patients on peritoneal dialysis.

De Jong et al included peritoneal dialysis patients in their study with 34% of the cohort being on Peritoneal Dialysis [21]. The proportion of patients in the cohort who suffered from a stroke was 28%. When stratifying for dialysis modality there was a slight improvement in discrimination for haemodialysis and a slight decrease for peritoneal dialysis, overall they reported the performance of these scores as poor.

Chan et al [22] studied peritoneal dialysis patients only and found very similar incidence of stroke for both low and high-risk patients, whereby risk stratification was performed with CHA_2DS_2VASc.

There remains a dire need for a well validated clinical risk score for estimating stroke risk in patients with non-valvular atrial fibrillation in patients with renal impairment. This need is most evident in patients who have end stage disease on renal replacement therapy due to the concerning observational evidence regarding risk of increased morbidity with a lack of efficacy in stroke risk or mortality reduction when treated with therapeutic anticoagulation [23, 24,25,26].

Biomarkers for stroke

More recent studies have explored the link between circulating stroke biomarkers and risk of stroke in patients with AF who are taking anticoagulation. N-terminal pro–B-type natriuretic peptide (NTproBNP) and growth differentiation factor 15 (GDF-15) were both shown to be positively associated with an increased risk of a stroke [27]. Participants from REasons for Geographic And Racial Differences in Stroke (REGARDS) study with AF not taking anticoagulants were used to assess the predictive ability of stroke when these biomarkers were added to CHA_2DS_2VASc, 5-year NRI>0 0.42 [28]. These studies are not specific to those with CKD but it may be that identifying biomarkers associated with stroke in CKD may also improve risk score predictive ability in this population. Nonetheless, biomarkers (whether blood, urine, imaging) will always improve stroke risk stratification based on clinical risk factors. Also, many biomarkers are influenced by renal impairment and vary with age and changing comorbidities or drug therapies, often being more reflective of a sick patient or a sick heart.

Practice recommendations

CHA_2DS_2VASc is an option for assessing stroke risk in patients with chronic kidney disease stage 4 with the knowledge that the score may underestimate stroke risk. **2B**

In patients with CKD stage 5 or those on dialysis the decision for stroke prophylaxis is nuanced. We suggest that stroke risk scores are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF. **2D**

Research recommendations

- Validation and/or optimisation of current stroke risk scores for patients with advanced kidney disease.
- Development of a stroke risk score specific for patients on renal replacement therapy

- Assessment of whether there are any biomarkers in patients with AF and CKD that may improve risk score predictability.

References

1. Randhawa MS, Vishwanath R, Rai MP, et al. Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(4):e202175-e202175. doi:10.1001/jamanetworkopen.2020.2175
2. Parker K, Hartemink J, Saha A, et al. A systematic review of the efficacy and safety of anticoagulants in advanced chronic kidney disease. *J Nephrol*. 2022;35(8):2015-2033. doi:10.1007/s40620-022-01413-x
3. Perry M, Kemmis Betty S, Downes N, Andrews N, Mackenzie S; Guideline Committee. Atrial fibrillation: diagnosis and management-summary of NICE guidance. BMJ. 2021 May 21;373:n1150
4. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(1):e1-e156. doi:10.1161/CIR.0000000000001193 .
5. Wang Y, Guo Y, Qin M, Fan J, Tang M, Zhang X, Wang H, Li X, Lip GYH; Expert Reviewers. 2024 Chinese Expert Consensus Guidelines on the Diagnosis and Treatment of Atrial Fibrillation in the Elderly, Endorsed by Geriatric Society of Chinese Medical Association (Cardiovascular Group) and Chinese Society of Geriatric Health Medicine (Cardiovascular Branch): Executive Summary. Thromb Haemost. 2024 Oct;124(10):897-911.
6. Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K, Lip GYH. 2021 Focused update of the 2017 consensus guidelines of the Asia Pacific Heart Rhythm Society (APHRS) on stroke prevention in atrial fibrillation. J Arrhythm. 2021 Nov 13;37(6):1389-1426.
7. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, De Potter TJR, Dwight J, Guasti L, Hanke T, Jaarsma T, Lettino M, Løchen ML, Lumbers RT, Maesen B, Mølgaard I, Rosano GMC, Sanders P, Schnabel RB, Suwalski P, Svennberg E, Tamargo J, Tica O, Traykov V, Tzeis S, Kotecha D; ESC Scientific Document Group. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024 Sep 29;45(36):3314-3414.
8. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Liao JN, Chen TJ, Lip GY, Chen SA. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart Rhythm. 2014 Oct;11(10):1752-9.
9. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM, Sanders GD. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. Thromb Haemost. 2018 Dec;118(12):2171-2187.
10. Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4):S117-S314. doi:10.1016/j.kint.2023.10.018
11. Bansal VK, Herzog CA, Sarnak MJ, et al. Oral Anticoagulants to Prevent Stroke in Nonvalvular Atrial Fibrillation in Patients With CKD Stage 5D: An NKF-KDOQI Controversies Report. *Am J Kidney Dis Off J Natl Kidney Found*. 2017;70(6):859-868. doi:10.1053/j.ajkd.2017.08.003

12. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72.
13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001 Jun 13;285(22):2864-70.
14. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Oto A, Mantovani LG, Misselwitz F, Piccini JP, Turpie AGG, Verheugt FWA, Kakkar AK; GARFIELD-AF Investigators. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open. 2017 Dec 21;7(12):e017157.
15. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc. 2013 Jun 21;2(3):e000250.
16. Roldán V, Marín F, Manzano-Fernandez S, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? *Thromb Haemost*. 2013;109(5):956-960. doi:10.1160/TH13-01-0054
17. Nakamura F, Nishimura K, Watanabe M, et al. Stroke risk assessment tool including chronic kidney disease improve a predictive probability: Fumiaki Nakamura. *Eur J Public Health*. 2015;25(suppl_3):ckv175-171.
18. Piccini JP, Stevens SR, Chang Y, et al. Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation. *Circulation*. 2013;127(2):224-232. doi:10.1161/CIRCULATIONAHA.112.107128
19. de Jong Y, Fu EL, van Diepen M, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. *Eur Heart J*. 2021;42(15):1476-1485. doi:10.1093/eurheartj/ehab059
20. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010;77(12):1098-1106. doi:10.1038/ki.2009.477
21. de Jong Y, Ramspek CL, van der Endt VHW, et al. A systematic review and external validation of stroke prediction models demonstrates poor performance in dialysis patients. *J Clin Epidemiol*. 2020;123:69-79. doi:10.1016/j.jclinepi.2020.03.015
22. Chan PH, Huang D, Yip PS, et al. Ischaemic stroke in patients with atrial fibrillation with chronic kidney disease undergoing peritoneal dialysis. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016;18(5):665-671. doi:10.1093/europace/euv289
23. Li J, Wang L, Hu J, Xu G. Warfarin use and the risks of stroke and bleeding in hemodialysis patients with atrial fibrillation: A systematic review and a meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases. 2015 Aug 1;25(8):706-13.
24. Dahal, K., Kunwar, S., Rijal, J., Schulman, P., & Lee, J. (2016). Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. Chest, 149(4), 951-959.
25. Liu, G., Long, M., Hu, X., Hu, C. H., Liao, X. X., Du, Z. M., & Dong, Y. G. (2015). Effectiveness and safety of warfarin in dialysis patients with atrial fibrillation: a meta-analysis of observational studies. Medicine, 94(50), e2233.
26. Nochaiwong S, Ruengorn C, Awiphan R, Dandecha P, et al. Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis: Open Heart 2016;3:e000441.

27. Short SAP, Hald E, Wilkinson K, Howard G, Howard V, Judd SE, Soliman EZ, Kissela B, Robinson D, Stanton R, Cushman M. Circulating biomarkers and ischemic stroke risk in adults with atrial fibrillation taking anticoagulation: the Reasons for Geographic And Racial Differences in Stroke study. J Thromb Haemost. 2025 Aug 1:S1538-7836(25)00353-8.
28. Short SAP, Wilkinson K, Hald E, Howard G, Howard V, Judd SE, Soliman EZ, Kissela B, Robinson D, Stanton R, Cushman M. Improving stroke risk prediction in atrial fibrillation with circulating biomarkers: the CHA2DS2-VASc-Biomarkers model. J Thromb Haemost. 2025 Aug 1:S1538-7836(25)00390-3.

Section 3b. The use of bleeding risk scores

Several bleeding assessment tools (such as the ORBIT, HAS-BLED, HEMORR$_2$HAGES, ATRIA bleeding risk scores) have been developed to determine major bleeding risk in the general population with AF [(1)]. In patients with atrial fibrillation (AF), the HAS-BLED score is the best validated and recommended in major guidelines [(1-4)]. However, these bleeding risk scores have limited validation in patients with advanced renal disease (CKD4-G5D), though renal impairment features in all these scores, table 4. For example, in the study by Ocak et al on 1745 dialysis patients, 183 patients had a bleeding event, corresponding to an incidence rate of 5.23/100 person-years. Ocak's study found that HAS-BLED [C-statistic of 0.58 (95% CI 0.54-0.62)], ATRIA [C-statistic of 0.55 (95% CI 0.51-0.60)], HEMORR$_2$HAGES [C-statistic of 0.56 (95% CI 0.52-0.61)] and ORBIT [C-statistic of 0.56 (95% CI 0.52-0.61)] risk scores all had poor discriminative performances in dialysis patients [(5)].

Even though the specific use of these scores somewhat varies between society guidelines, their use helps to draw attention to modifiable risk factors and to identify patients at high bleeding risk earlier in the shared decision-making process. This is important since bleeding is the interaction of modifiable and nonmodifiable bleeding risk factors, and is not static but dynamic in nature, changing with any changes in comorbidities [(6)].

Table 4: Bleeding risk scores

	HASBLED [7]	ORBIT [8]	HAEMORR$_2$HAGES [9]	ATRIA [10]	DOAC score [11]
Hypertension	√		√	√	√
Renal disease	√	√	√	+3	+1 to +2
Liver disease	√		√		+2
Stroke	√		√		√
Bleeding history	√	+2	+2	√	+3
Age	√	√	√	+2	+2 to +5
Other medication predisposing to bleeding	√	√	√		+1 to +3
Alcohol	√		√		
Labile INR	√				
Anaemia		+2	√	+3	
Malignancy			√		
Reduced platelet count or function (includes antiplatelet)			√		
Genetic factors (CYP 2C9 single-nucleotide polymorphisms)			√		
Excessive falls risk			√		
Low BMI					√
Diabetes					√
High risk score	≥3	≥4	≥4	≥4	≥8

ORBIT: Older age, Reduced haemoglobin, Bleeding history, Insufficient kidney function, Treatment with antiplatelets; INR: International Normalised Ratio; TTR: time in therapeutic range; HAS-BLED: Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol; eGFR: estimated glomerular filtration rate; CYP: cytochrome P; HEMORR$_2$HAGES: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding risk, hypertension, anaemia, genetic factors, excessive fall risk, stroke.

ORBIT bleeding score

O'Brien et al developed and validated the ORBIT score by using prospective registry data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) and the Rivaroxaban Once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF) [8,12]. It performed well in predicting bleeding risk in individuals with mild to moderate CKD (CKD 1-3), it has not been validated for use in patients with NVAF and advanced kidney disease (CKD 4-5D).

Several studies have shown that ORBIT was not superior to HAS-BLED in predicting major bleeding [13-20]. The ORBIT risk score may underestimate the risk of major bleeding events in anticoagulated patients with AF [15, 16, 21]. Other studies have similarly found no advantage of the ORBIT over HAS-BLED score for bleeding risk prediction, even in DOAC users [7, 15, 22, 23].

HAS-BLED score

The HAS-BLED score is the bleeding risk score recommended by guidelines for the estimation of major bleeding risk in the general population with non-valvular AF given its simplicity, its validation in various cohorts (European and globally) and anticoagulated AF trial cohorts [24, 25], and its relatively higher discrimination. Overall, evidence indicates that HAS-BLED is superior to the ORBIT, ATRIA and HEMORR2HAGES bleeding risk scores in predicting clinically relevant bleeding events, including intra-cranial haemorrhage, amongst patients with AF on anticoagulation [2, 17, 18, 26-31]. It is also the best score at predicting bleeding risk in patients on maintenance HD [25].

Both ATRIA and ORBIT categorised more patients as low-risk for major bleeding when compared with HAS-BLED, also, HAS-BLED has higher sensitivity (62.8%) but lower specificity for major bleeding risk when compared to the ORBIT score (37.1%) and ATRIA (29.7%) [14]. The HAS-BLED score provided most benefit if a major bleeding risk threshold between 1.7-2% is applied, while the benefit from using either ATRIA or ORBIT score was only evident using a threshold between 2-6% [14]. A recent study in NVAF patients receiving DOACs, the HAS-BLED score showed an ability to predict major bleeding comparable to that of the DOAC score and superior to that of the ORBIT score [23].

HEMORR$_2$HAGES risk score

The HEMORR$_2$HAGES risk score was developed using the National Registry of Atrial Fibrillation data set [9]. Its use is suggested by the KDIGO and ACC/AHA guidelines, along other risk scores. The genetic factor (CYP 2C9 single nucleotide polymorphisms) criterion is rarely readily available in daily clinical practice and may arguably underestimate bleeding risk if left out of the score. Nonetheless, it can be used as an aide-memoire during the holistic assessment of bleeding risk as it includes conditions which are absent in the other risk scores e.g. malignancy, thrombocytopenia, excessive fall risk and stroke. Its ability to predict major bleeding risk as compared to other scores is discussed above.

ATRIA

The ATRIA bleeding risk score was developed by Fang et al in 2011 [10] and reported a C statistic of 0.74. It assigns the highest number of points to those with severe renal failure, including dialysis patients. The features included in the ATRIA score are all found in the HAS-BLED, HEMORR$_2$HAGES and ORBIT scores, and therefore it adds little to the general assessment of bleeding risk when compared to using the other available scores. Its comparison to the other available bleeding risk scores is discussed above.

Other risk models and novel approaches

The BLEED-HD risk equation was recently developed using data from the DOPPS cohort to predict bleeding risk in the general haemodialysis population. BLEED-HD consists of 6 risk factors for major bleeding: age, sex, previous gastrointestinal bleeding, presence of a prosthetic heart valve, vitamin K antagonist use and country of origin, as haemorrhagic events were higher in Europe, North America, Australia and New Zealand. The BLEED-HD model yielded a superior discrimination index and calibration (C statistic of 0.65) than that demonstrated by the HAS-BLED, ATRIA and HEMORR$_2$HAGES (C statistic <0.6). Though it is an attractive novel tool validated for use in HD patients, its use has not been applied to HD patients with underling AF to date [32].

The use of artificial intelligence (AI) and data science develop predictive modelling schemes remains in its embryonic stage, though it is predicted to change the landscape of research in healthcare. Nopp et al employed machine learning-based prediction models to identify novel approaches and predictors of bleeding risk assessment in an HD cohort based on general clinical parameters but failed to supersede the currently available risk scores in predicting bleeding events [31].

High risk groups

History of previous haemorrhagic episodes on bleeding risk

Previous history of bleeding is consistently featured in several bleeding risk scores (table 3) as it remains a strong predictor for bleeding, irrespective of renal function. A previous DOPPS study confirmed that a history of gastrointestinal bleeding was the sole strongest risk factor for predicting future bleeding risk [33]. A Swedish register-based cohort study including patients with advanced CKD (CKD 3-5D) with AF on oral anticoagulants (warfarin or DOAC) further demonstrated that CKD5 – 5D vs CKD3 (HR 1.92, 95% CI 1.43–2.56) and previous major bleeding event (gastrointestinal (HR 1.77, 95% CI 1.39–2.25) or other bleeding event (HR 1.33, 95% CI 1.09–1.62) are strongly associated with a high bleeding risk. Moreover, male sex (HR 1.28, 95% CI 1.03–1.60), congestive heart failure (HR 1.36, 95% CI 1.11–1.68) and vascular disease (HR 1.35, 95% CI 1.01–1.79) were also associated with an increased bleeding risk during oral-anticoagulation [34].

Ongoing antiplatelet use

The heightened risk of bleeding with the combined use of anticoagulation and antiplatelet therapy is well documented in the literature. An analysis of patients suffering an intracranial haemorrhage in the ARISTOTLE study revealed that such patients were usually older, were more likely to suffer from CKD at baseline, and received aspirin concomitantly with warfarin [35]. A Danish study reported an incremental increase in bleeding risk among patients with renal disease and AF when treated with warfarin (HR 1.33; P<0.001) or combined warfarin and aspirin (HR 1.61; P<0.001) [36]. A Canadian study revealed that among HD patients who were not exposed to VKA or antiplatelet agents, the risk of major bleeding episodes per year of exposure was 0.8%. This risk rose exponentially to 3.1, 4.4, and 6.3% in those HD patients receiving warfarin alone, aspirin alone, or receiving both warfarin and aspirin, respectively [37]. Therefore, the indications and risk-benefit ratio of combined anticoagulation and antiplatelet therapy should be evaluated thoroughly prior to prescribing, especially in such a high-risk population.

Previous acute coronary syndrome

The ACC/AHA/ACCP/HRS guidelines recommend that patients with NVAF and an increased risk of stroke who undergo percutaneous coronary intervention, DOAC use is preferred over warfarin in combination with antiplatelet therapy due to the lower risk of bleeding events [38]. Randomised controlled trials in AF patients with CKD4-5D suffering from ACS are yet to be performed to further guide management. Nonetheless, the duration of combined anticoagulant and single or dual antiplatelet therapy needs to be minimized due to the inadvertent higher risk of bleeding and must be individualized according to clinical factors and type of stent used.

Summary

In patients with advanced renal impairment, the combined use of currently available stroke and bleeding risk scores, together with a thorough holistic assessment of comorbidities is encouraged to assist in the shared decision-making process. Identifying novel predictors of bleeding pertaining specifically to people with advanced CKD and improving current methods of risk stratification are important areas of further investigation. Assessment of the risk-to-benefit ratio of anticoagulant use should be evaluated regularly throughout the course of therapy given that bleeding and stroke risk is dynamic, with the involvement of the multidisciplinary team in complex situations.

Practice recommendations

We suggest that bleeding scores are not to be used in isolation but should be included in the holistic assessment of the patient to facilitate shared decision making regarding thromboprophylaxis in AF, and to identify particularly high bleeding risk patients for early review and follow up. **2D**

Audit and research recommendations:

- Development of a validated bleeding risk score to allow risk stratification in patients with non-dialysis dependent advanced CKD (CKD 4 – 5) with NVAF.
- A formal assessment of the utility of a validated haemodialysis-specific bleeding risk score to allow risk stratification in patients with ESKD on haemodialysis with NVAF.
- Development of a validated peritoneal dialysis-specific bleeding risk score to allow risk stratification in patients with ESKD on peritoneal dialysis with NVAF.
- Randomised control trials evaluating the safety and efficacy of anticoagulation in patients with ESKD on dialysis and non-valvular AF by means of dialysis-specific bleeding and thromboembolic risk scores.
- Development of bleeding risk models with the judicious use of AI technologies to allow risk stratification in patients with advanced CKD, including those on dialysis.

References

1. Borre ED, Goode A, Raitz G, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost*. 2018;118(12):2171-2187. doi: 10.1055/s-0038-1675400.
2. Gorog DA, Gue YX, Chao TF, Fauchier L, Ferreiro JL, Huber K, Konstantinidis SV, Lane DA, Marin F, Oldgren J, Potpara T, Roldan V, Rubboli A, Sibbing D, Tse HF, Vilahur G, Lip GYH. Thromb Haemost. 2022;122(10):1625-1652.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. doi: 10.1093/eurheartj/ehaa612. Erratum in: Eur Heart J. 2021 Feb

1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546-547. Erratum in: Eur Heart J. 2021 Oct 21;42(40):4194. PMID: 32860505.

4. Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K, Lip GYH. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thromb Haemost.* 2022;122(1):20-47.
5. Ocak G, Ramspek C, Rookmaaker MB, et al. *Nephrol Dial Transplant.* 2019;34(7):1223-1231.
6. Serna MJ, Rivera-Caravaca JM, López-Gálvez R, Soler-Espejo E, Lip GYH, Marín F, Roldán V. Dynamic assessment of CHA2DS2-VASc and HAS-BLED scores for predicting ischemic stroke and major bleeding in atrial fibrillation patients. Rev Esp Cardiol (Engl Ed). 2024 Oct;77(10):835-842.
7. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-100. doi: 10.1378/chest.10-0134. Epub 2010 Mar 18. PMID: 20299623.
8. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J.* 2015;36(46):3258- 64. doi: 10.1093/eurheartj/ehv476.
9. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151(3):713-9. doi: 10.1016/j.ahj.2005.04.017. PMID: 16504638.
10. Fang MC, Go AS, Chang Y, et al. A New Risk Scheme to Predict Warfarin-Associated Hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol.* 2011;58(4):395-401. doi:10.1016/j.jacc.2011.03.031

11. Aggarwal R, Ruff CT, Virdone S, Perreault S, Kakkar AK, Palazzolo MG, Dorais M, Kayani G, Singer DE, Secemsky E, Piccini J, Tahir UA, Shen C, Yeh RW. Development and Validation of the DOAC Score: A Novel Bleeding Risk Prediction Tool for Patients With Atrial Fibrillation on Direct-Acting Oral Anticoagulants. Circulation. 2023 Sep 19;148(12):936-946.
12. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J.* 2011;162(4):606 e1–612 e1.
13. Guo Y, Zhu H, Chen Y, Lip GYH. Comparing Bleeding Risk Assessment Focused on Modifiable Risk Factors Only Versus Validated Bleeding Risk Scores in Atrial Fibrillation. *Am J Med.* 2018;131(2):185-192. doi: 10.1016/j.amjmed.2017.09.009. Epub 2017 Sep 21. PMID: 28943382.
14. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med.* 2018;131(5):574.e13-574.e27.
15. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget*. 2017;8(65):109703-109711.
16. Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin. *Am J Med*. 2016;129(6):600-7. doi: 10.1016/j.amjmed.2015.10.001.
17. Esteve-Pastor MA, García-Fernández A, Macías M, Sogorb F, Valdés M, Roldán V, Muñiz J, Badimon L, Roldán I, Bertomeu-Martínez V, Cequier Á, Lip GY, Anguita M, Marín F; FANTASIIA Investigators. Is the ORBIT Bleeding Risk Score Superior to the HAS-BLED Score in

Anticoagulated Atrial Fibrillation Patients? *Circ J*. 2016;80(10):2102-8. doi: 10.1253/circj.CJ-16-0471.

18. Yao X, Gersh BJ, Sangaralingham LR, Kent DM, Shah ND, Abraham NS, Noseworthy PA. Comparison of the CHA_2DS_2-VASc, $CHADS_2$, HAS-BLED, ORBIT, and ATRIA Risk Scores in Predicting Non-Vitamin K Antagonist Oral Anticoagulants-Associated Bleeding in Patients With Atrial Fibrillation. *Am J Cardiol.* 2017 ;120(9):1549-1556. doi: 10.1016/j.amjcard.2017.07.051. Epub 2017 Jul 31. PMID: 28844514.
19. Wattanaruengchai P, Nathisuwan S, Karaketklang K, Wongcharoen W, Phrommintikul A, Lip GYH. Comparison of the HAS-BLED versus ORBIT scores in predicting major bleeding among Asians receiving direct-acting oral anticoagulants. *Br J Clin Pharmacol.* 2022;88(5):2203-2212. doi: 10.1111/bcp.15145. Epub 2021 Dec 15. PMID: 34783372.
20. Proietti M, Romiti GF, Vitolo M, Potpara TS, Boriani G, Lip GYH. Comparison of HAS-BLED and ORBIT bleeding risk scores in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants: a report from the ESC-EHRA EORP-AF General Long-Term Registry. *Eur Heart J Qual Care Clin Outcomes.* 2022;26;8(7):778-786. doi: 10.1093/ehjqcco/qcab069. Erratum in: *Eur Heart J Qual Care Clin Outcomes*. 2023;9(4):437.
21. Chichareon P, Winijkul A, Lip GYH, Krittayaphong R. Comparative validation of HAS-BLED, GARFIELD-AF and ORBIT bleeding risk scores in Asian people with atrial fibrillation treated with oral anticoagulant: A report from the COOL-AF registry. *Br J Clin Pharmacol.* 2023;89(8):2472-2482. doi: 10.1111/bcp.15716.
22. Esteve-Pastor MA, Rivera-Caravaca JM, Roldán V, et al. Predicting performance of the HAS-BLED and ORBIT bleeding risk scores in patients with atrial fibrillation treated with Rivaroxaban: Observations from the prospective EMIR Registry. *Eur Heart J Cardiovasc Pharmacother*. 2022;9(1):38-46. doi: 10.1093/ehjcvp/pvac060. PMID: 36318457.
23. Fan M, Yin X, Jin Y, Zheng X, Zhu S. Assessing the applicability of the DOAC, HAS-BLED and ORBIT risk scores in Chinese patients on non-vitamin K antagonist oral anticoagulants. Br J Clin Pharmacol. 2025; 1-11.
24. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57(2):173-80. doi: 10.1016/j.jacc.2010.09.024. Epub 2010 Nov 24. PMID: 21111555.
25. Nopp S, Spielvogel CP, Schmaldienst S, Klauser-Braun R, Lorenz M, Bauer BN, Pabinger I, Säemann M, Königsbrügge O, Ay C. Bleeding Risk Assessment in End-Stage Kidney Disease: Validation of Existing Risk Scores and Evaluation of a Machine Learning-Based Approach. *Thromb Haemost*. 2022;122(9). doi: 10.1055/a-1754-7551.
26. Roldán V, Marín F, Fernández H, Manzano-Fernandez S, Gallego P, Valdés M, Vicente V, Lip GYH. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. *Chest*. 2013;143(1):179-184. doi: 10.1378/chest.12-0608. PMID: 22722228.
27. Fauchier L, Chaize G, Gaudin AF, Vainchtock A, Rushton-Smith SK, Cotté FE. Predictive ability of HAS-BLED, HEMORR2HAGES, and ATRIA bleeding risk scores in patients with atrial fibrillation. A French nationwide cross-sectional study. *Int J Cardiol*. 2016;217:85-91. doi: 10.1016/j.ijcard.2016.04.173.
28. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J Am Coll Cardiol*. 2012 Aug 28;60(9):861-7. doi: 10.1016/j.jacc.2012.06.019. Epub 2012 Aug 1. PMID: 22858389

29. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischemic stroke and bleeding in 182,678 patients with atrial fibrillation: The Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500-10.
30. Guo YT, Zhang Y, Shi XM, Shan ZL, Wang CJ, Wang YT, Chen YD, Lip GY. Assessing bleeding risk in 4824 Asian patients with atrial fibrillation: The Beijing PLA Hospital Atrial Fibrillation Project. *Sci Rep*. 2016;6:31755.
31. Sab M, Chelala D, Aoun M, Azar R, Abdel Massih T. Stroke in hemodialysis patients and its association with CHA_2DS_2-VASC and HAS-BLED scores: a retrospective study. *Clin Kidney J.* 2022;16(3):596-602. doi: 10.1093/ckj/sfac260. PMID: 36865009; PMCID: PMC9972838.
32. Madken M, Mallick R, Rhodes E, Mahdavi R, Bader Eddeen A, Hundemer GL, Kelly DM, Karaboyas A, Robinson B, Bieber B, Molnar AO, Badve SV, Tanuseputro P, Knoll G, Sood MM. Development and Validation of a Predictive Risk Algorithm for Bleeding in Individuals on Long-term Hemodialysis: An International Prospective Cohort Study (BLEED-HD). *Can J Kidney Health Dis*. 2023;10:20543581231169610. doi: 10.1177/20543581231169610.
33. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013;84(3):600-8. doi: 10.1038/ki.2013.170.
34. Welander F, Renlund H, Själander A, Risk factors for major bleeding in patients with atrial fibrillation and CKD G3–G5D on oral anticoagulants, Clinical Kidney Journal, Volume 17, Issue 8, August 2024, sfae206, https://doi.org/10.1093/ckj/sfae206
35. Lopes RD, Guimarães PO, Kolls BJ, Wojdyla DM, Bushnell CD, Hanna M, Easton JD, Thomas L, Wallentin L, Al-Khatib SM, Held C, Gabriel Melo de Barros E Silva P, Alexander JH, Granger CB, Diener HC. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood*. 2017;129(22):2980-2987. doi: 10.1182/blood-2016-08-731638.
36. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012 Aug 16;367(7):625-35. doi: 10.1056/NEJMoa1105594. Erratum in: N Engl J Med. 2012 Dec 6;367(23):2262. PMID: 22894575.
37. Holden RM, Harman GJ, Wang M, Holland D, Day AG. Major bleeding in hemodialysis patients. *Clin J Am Soc Nephrol.* 2008;3(1):105-10. doi: 10.2215/CJN.01810407.
38. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):e1-e156. doi: 10.1161/CIR.0000000000001193

Section 4: Treatment options for NVAF thromboprophylaxis

Section 4a - Anticoagulation vs no anticoagulation

CKD 4 and non-dialysis dependent CKD 5

Oral anticoagulation is a common clinical practice for managing NVAF in patients with CKD stage 4 and 5, and both VKAs and DOACs are routinely prescribed in this patient population [1]. However, the existing evidence is limited to observational data [2].

Five observational cohort studies, only one of which was prospective, are discussed within this guideline (supplementary Table 1). Several other studies include patients with CKD 4 and 5 in larger cohorts of patients with CKD, but as individual patient-level CKD staging was not available, subgroup analyses for CKD 4 and 5 were not performed in these studies [3, 4]. Of note, the Stroke Prevention in Atrial Fibrillation III Study included patients with creatinine up to 3 mg/dL (265 µmol/L). Only thirty (2%) of the 1936 patients were categorised as CKD 4 and thus a meaningful sub group analysis is not possible [5].

The observational studies that are included here investigated the efficacy and safety profiles of DOACs or VKA in comparison to no anticoagulation [6-9]. The clinical outcomes reported were predominantly ischaemic stroke, major bleeding, and survival.

The largest of these studies included data on over 12,000 patients from three Swedish national healthcare registries [8]. Using adjusted analyses, they found that warfarin significantly reduced the risk of ischaemic stroke in patients with CKD 4 (HR 0.53, 95% CI 0.38-0.74) and a significant reduction in mortality (HR 0.45, 95% CI 0.40-0.51). In CKD 5, warfarin-treated patients had no significant difference in the risk of stroke compared to no anticoagulation but there was a higher risk of major bleeding (HR 1.52, 95% CI 1.15-2.01). However, all-cause mortality was lower with those treated with warfarin (HR 0.44, 95% CI 0.36-0.54).

Another large study from Taiwan, involving 3,771 patients, conducted adjusted analyses that demonstrated a higher risk of ischaemic stroke or systemic embolism in the warfarin group compared to no treatment (aHR 3.1, 95% CI 2.1-4.6) [7]. In contrast, no significant difference was observed between DOAC-treated patients and those not receiving anticoagulation (aHR 1.1, 95% CI 0.3-3.5). Both warfarin (aHR 2.8, 95% CI 2.0-3.8) and DOAC (aHR 3.1, 95% CI 1.9-5.2) use were associated with increased rates of major bleeding. Mortality was notably higher among warfarin-treated patients with CKD 5 compared to no anticoagulation, although no significant effect was observed with DOACs. Similar trends were found in subgroup analyses of CKD 4 and 5, despite there being limited DOAC-treated patients with CKD 5.

While there is some evidence supporting the benefits of anticoagulation in patients with AF and CKD in general, high-quality evidence specifically addressing patients with CKD 4 and non-dialysis-dependent CKD 5 is clearly lacking. Existing evidence is predominantly derived from non-randomised studies, which are highly susceptible to selection bias despite adjustments for confounders. Moreover, retrospective observational methodologies are likely to underestimate the occurrence of adverse events, particularly non-major bleeding. This highlights the need for further Randomised Controlled Trials (RCT) data to guide current NVAF management in patients with advanced CKD. It is

acknowledged that financial and practical constraints present the ongoing challenges to conducting RCTs. However, target trial emulation (TTE) is emerging as a powerful observational research methodology due to its advantages in addressing confounders, handling time-varying covariates, and enabling causal inference. A notable example is a French study that employed TTE using the French Renal Epidemiology and Information Network (REIN) registry to evaluate the comparative efficacy and safety of DOACs versus VKAs [10]. While this study did not explore the effects of anticoagulation against no treatment, TTE holds promise as a novel approach for assessing the comparative efficacy and safety of DOACs or VKAs compared to no anticoagulation in this patient population.

Dialysis-dependent CKD 5 (CKD 5D)

Three RCTs - Valkyrie, RENAL-AF, and AXADIA-AFNET 8 - have evaluated either the use of apixaban or rivaroxaban in the dialysis population [11-13]. These studies, however, focused on comparing their efficacy and safety to VKAs. There are currently no RCTs that have directly compared DOACs versus no anticoagulation in this patient cohort. Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients with Atrial Fibrillation (SACK; NCT05679024) and Strategies for the Management of Atrial Fibrillation in patiEnts receiving Dialysis (SAFE-D; NCT03987711) are two ongoing RCTs investigating the effects of DOACs versus no anticoagulation, but the results are still awaited .

Twelve observational studies investigated the use of VKAs compared to no anticoagulation in HD patients (Supplementary Table 2), while two studies specifically examined the efficacy and safety of VKAs in PD patients (Supplementary Table 3). In addition, six studies investigated oral anticoagulation therapy in both dialysis modalities, including one study on apixaban and five on VKAs (Supplementary Table 4). Three studies did not specify the dialysis modality of their study populations (Supplementary Table 5). As with other observational studies, the results of these analyses face significant limitations in establishing causal relationships. A recent systematic review by Parker et al found that the majority of these studies have a moderate to serious risk of bias based on the ROBINS-I assessment, further highlighting the challenges of applying findings from current observational evidence in clinical practice [14]. Here we provide an overview of the retrospective studies with a low risk of bias.

A Swedish registry study assessed 12,106 patients, including 2,971 on HD and 1,208 on PD [8]. Sensitivity analysis was conducted using Cox regression to adjust for dialysis modality, with quantitative variables modelled as restricted cubic splines. The findings indicated that warfarin treatment was associated with a lower risk of ischaemic stroke (HR 0.49; 95% CI 0.30-0.79), but a higher risk of major bleeding (HR 1.23; 95% CI 1.00-1.51) [8].

Tan et al evaluated the outcomes of warfarin treatment compared to no anticoagulation in both HD and PD patients using inverse probability of treatment weighting in Cox regression to account for time-varying use of warfarin. They found no significant risk reduction in ischaemic stroke (HR 0.88; 95% CI 0.70-1.11), but an increased risk of major bleeding (HR 1.50; 95% CI 1.33-1.68) [15].

A propensity-matched cohort study investigated the effects of apixaban for managing NVAF in patients undergoing both HD and PD [16]. The study assessed the effects of apixaban using both dosing of 5mg BD and 2.5mg BD. The findings showed that apixaban, compared to no

anticoagulation, was associated with a significantly higher rate of fatal or intracranial bleeding (HR 2.74; 95% CI 1.37-5.47) but with no significant difference in hospitalisation from SSE.

A study of 22,771 veterans (95% male) in the United States (US) with ESKD who developed AF before starting dialysis [17]. Warfarin-treated patients were generally younger, had lower CHA_2DS_2-VASc scores, fewer comorbidities, but were more likely to be on a range of cardiovascular disease-modifying medications. Multivariable Cox regression analysis showed a reduction in all-cause mortality, but an increased risk of stroke or TIA requiring hospitalisation and major bleeding.

Two studies used propensity score matching to evaluate the effects of oral anticoagulation on dialysis patients in their retrospective cohorts (Supplementary Table 5) [18, 19]. The first study reported that oral anticoagulation reduced the risks of all-cause mortality (HR 0.67; 95% CI 0.55-0.81) and ischaemic stroke (HR 0.61; 95% CI 0.41-0.89). See et al elucidated that oral anticoagulation was associated with a higher risk of ischaemic stroke or systemic embolism (HR 1.54; 95% CI 1.29-1.84), with no difference in efficacy and safety outcomes between VKAs and DOACs.

There are two retrospective cohort studies of warfarin-treatment that include PD patients, Supplementary Table 3 [20, 21]. Phan [2019] found no statistically significant differences in clinical outcomes between the warfarin group and non-anticoagulated group [20]. In contrast, Chan [2016] reported that warfarin treatment was associated with a lower risk of ischaemic stroke compared to no treatment (HR 0.19; 95% CI 0.06-0.65; p = 0.01), without increasing the risk of intracranial haemorrhage [21]. Nonetheless, both studies were subject to small sample sizes, significant bias, and the lack of longitudinal outcome data, making it difficult to draw causal inferences. This highlights the ongoing challenges in studying this specific patient cohort.

Summary

The effects of anticoagulation on clinical outcomes, compared to no anticoagulation, in dialysis patients exhibit considerable variability across the identified studies. While propensity score matching is often used in observational studies to improve the estimation of treatment effects, it can overestimate these effects when significant confounding is present. Additionally, selection bias arising from clinicians' prescribing preferences for initiating oral anticoagulation further complicate the interpretation of findings.

Similar to findings from the existing meta-analyses warfarin therapy has not been shown to significantly reduce mortality, stroke and thromboembolism risk [25-28], but is associated with an increased risk of major bleeding, particularly haemorrhagic stroke [22-25]. Despite a trend suggesting warfarin might reduce ischaemic stroke risk, its overall protective effect remains unclear. The available evidence highlights the complexity of balancing thrombotic and bleeding risks in a highly heterogeneous patient population. While oral anticoagulation offers potential benefits, such as stroke prevention, a more nuanced and individualised to clinical decision-making is essential for weighing these benefits against the significant bleeding risks, particularly in dialysis patients.

Clinicians should carefully assess each case, considering patient-specific factors such as treatment adherence and informed preferences when tailoring treatment decisions. Multidisciplinary reviews are also integral to optimising patient outcomes. Given the current evidence, the decision to forgo anticoagulation is also a reasonable treatment strategy, provided patients are fully informed and involved in the decision-making process.

Practice recommendations

Anticoagulation should be considered as an option for NVAF thromboprophylaxis in patients with CKD stage 4, 5 and patients on dialysis. **2C**

Not offering any anticoagulation may be considered an option, particularly in those with CKD stage 5 CKD or on dialysis. **2C**

Research recommendations

- The efficacy of anticoagulation on mortality, stroke and thromboembolism risk reduction in patients with advanced CKD to determine specific patient groups that are likely to benefit from anticoagulation for NVAF thromboprophylaxis.

References

1. Parker K, Choudhuri S, Lewis P, Thachil J, Mitra S. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. BMC Nephrol. 2023;24(1):9.
2. Tan J, Liu S, Segal JB, Alexander GC, McAdams-DeMarco M. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. BMC Nephrol. 2016;17(1):157.
3. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367(7):625-35.
4. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. J Am Coll Cardiol. 2014;64(23):2471-82.
5. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(11):2599-604.
6. Chantrarat T, Krittayaphong R. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and chronic kidney disease in Asian Population, Data from the COOL-AF Thailand registry. Int J Cardiol. 2021;323:90-9.
7. Chang SH, Wu CV, Yeh YH, Kuo CF, Chen YL, Wen MS, et al. Efficacy and Safety of Oral Anticoagulants in Patients With Atrial Fibrillation and Stages 4 or 5 Chronic Kidney Disease. Am J Med. 2019;132(11):1335-43.e6.
8. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Efficacy and safety of warfarin in patients with non-valvular atrial fibrillation and CKD G3-G5D. Clin Kidney J. 2022;15(6):1169-78.
9. Lai HM, Aronow WS, Kalen P, Adapa S, Patel K, Goel A, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. Int J Nephrol Renovasc Dis. 2009;2:33-7.
10. Laville S, Couchoud C, Choukroun G, Liabeuf S. Effectiveness and safety of direct oral anticoagulants vs VKA in patients on chronic dialysis: a target trial emulation using nationwide registry data. Nephrology Dialysis Transplantation; 2024. p. 1662-71.
11. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. J Am Soc Nephrol. 2020;31(1):186-96.

12. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. Circulation. 2022;146(23):1735-45.
13. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, Gerß J, et al. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. Circulation. 2023;147(4):296-309.
14. Parker K, Hartemink J, Saha A, Mitra R, Lewis P, Power A, et al. A systematic review of the efficacy and safety of anticoagulants in advanced chronic kidney disease. J Nephrol. 2022;35(8):2015-33.
15. Tan J, Bae S, Segal JB, Zhu J, Alexander GC, Segev DL, et al. Warfarin use and the risk of stroke, bleeding, and mortality in older adults on dialysis with incident atrial fibrillation. Nephrology (Carlton). 2019;24(2):234-44.
16. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146-54.
17. Agarwal MA, Potukuchi PK, Sumida K, Naseer A, Molnar MZ, George LK, et al. Clinical Outcomes of Warfarin Initiation in Advanced Chronic Kidney Disease Patients With Incident Atrial Fibrillation. JACC Clin Electrophysiol. 2020;6(13):1658-68.
18. Kim DG, Kim SH, Park SY, Han BG, Kim JS, Yang JW, et al. Anticoagulation in patients with end-stage kidney disease and atrial fibrillation: a national population-based study. Clin Kidney J. 2024;17(2):sfae029.
19. See LC, Lee HF, Chao TF, Li PR, Liu JR, Wu LS, et al. Effectiveness and Safety of Direct Oral Anticoagulants in an Asian Population with Atrial Fibrillation Undergoing Dialysis: A Population-Based Cohort Study and Meta-Analysis. Cardiovasc Drugs Ther. 2021;35(5):975-86.
20. Phan D, Yang SJ, Shen AY, Lee MS. Effect of Warfarin on Ischemic Stroke, Bleeding, and Mortality in Patients with Atrial Fibrillation Receiving Peritoneal Dialysis. Am J Cardiovasc Drugs. 2019;19(5):509-15.
21. Chan PH, Huang D, Yip PS, Hai J, Tse HF, Chan TM, et al. Ischaemic stroke in patients with atrial fibrillation with chronic kidney disease undergoing peritoneal dialysis. Europace. 2016;18(5):665-71.
22. Van Der Meersch H, De Bacquer D, De Vriese AS. Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis. Am Heart J. 2017;184:37-46.
23. Nochaiwong S, Ruengorn C, Awiphan R, Dandecha P, Noppakun K, Phrommintikul A. Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis. Open Heart. 2016;3(1):e000441.
24. Lee M, Saver JL, Hong KS, Wu YL, Huang WH, Rao NM, et al. Warfarin Use and Risk of Stroke in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Meta-Analysis. Medicine (Baltimore). 2016;95(6):e2741.
25. Liu G, Long M, Hu X, Hu CH, Liao XX, Du ZM, et al. Effectiveness and Safety of Warfarin in Dialysis Patients With Atrial Fibrillation: A Meta-Analysis of Observational Studies. Medicine (Baltimore). 2015;94(50):e2233.
26. Sy J, Wenziger C, Marroquin M, Kalantar-Zadeh K, Kovesdy C, Streja E. Warfarin Use, Stroke, and Bleeding Risk among Pre-Existing Atrial Fibrillation US Veterans Transitioning to Dialysis. Nephron. 2022;146(4):360-8.
27. Wakasugi M, Kazama JJ, Tokumoto A, Suzuki K, Kageyama S, Ohya K, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. Clin Exp Nephrol. 2014;18(4):662-9.

28. Genovesi S, Rossi E, Gallieni M, Stella A, Badiali F, Conte F, et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. Nephrol Dial Transplant. 2015;30(3):491-8.
29. Kai B, Bogorad Y, Nguyen LN, Yang SJ, Chen W, Spencer HT, et al. Warfarin use and the risk of mortality, stroke, and bleeding in hemodialysis patients with atrial fibrillation. Heart Rhythm. 2017;14(5):645-51.
30. Yoon CY, Noh J, Jhee JH, Chang TI, Kang EW, Kee YK, et al. Warfarin Use in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Nationwide Population-Based Study. Stroke. 2017;48(9):2472-9.
31. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol. 2011;6(11):2662-8.
32. Akbar MR, Febrianora M, Iqbal M. Warfarin Usage in Patients With Atrial Fibrillation Undergoing Hemodialysis in Indonesian Population. Curr Probl Cardiol. 2023;48(5):101104.
33. Genovesi S, Rebora P, Gallieni M, Stella A, Badiali F, Conte F, et al. Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study. J Nephrol. 2017;30(4):573-81.
34. Garg L, Chen C, Haines DE. Atrial fibrillation and chronic kidney disease requiring hemodialysis - Does warfarin therapy improve the risks of this lethal combination? Int J Cardiol. 2016;222:47-50.
35. Mitsuma W, Matsubara T, Hatada K, Imai S, Saito N, Shimada H, et al. Clinical characteristics of hemodialysis patients with atrial fibrillation: The RAKUEN (Registry of atrial fibrillation in chronic kidney disease under hemodialysis from Niigata) study. J Cardiol. 2016;68(2):148-55.
36. Shen JI, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes After Warfarin Initiation in a Cohort of Hemodialysis Patients With Newly Diagnosed Atrial Fibrillation. Am J Kidney Dis. 2015;66(4):677-88.
37. Yodogawa K, Mii A, Fukui M, Iwasaki YK, Hayashi M, Kaneko T, et al. Warfarin use and incidence of stroke in Japanese hemodialysis patients with atrial fibrillation. Heart Vessels. 2016;31(10):1676-80.
38. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20(10):2223-33.
39. Wang TK, Sathananthan J, Marshall M, Kerr A, Hood C. Relationships between Anticoagulation, Risk Scores and Adverse Outcomes in Dialysis Patients with Atrial Fibrillation. Heart Lung Circ. 2016;25(3):243-9.
40. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation. 2014;129(11):1196-203.

Section 4b Anticoagulant versus anticoagulant

CKD stage 4

VKAs act by inhibiting the synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X). The pharmacokinetics are complex and exhibit significant variability, primarily due to hepatic metabolism via cytochrome P450 (CYP450) enzymes such as CYP2C9 [(1)]. VKAs have a slow onset of action and are subject to a great number of interactions with medications and food substances, necessitating regular INR monitoring to maintain therapeutic levels. In contrast, DOACs have very different

pharmacokinetic profiles. Apixaban, edoxaban, and rivaroxaban directly inhibit factor Xa to prevent thrombin formation, while dabigatran reversibly binds to thrombin to inhibit thrombin-mediated activation of the coagulation cascade [1]. DOACs offer several advantages, including more predictable pharmacokinetics and fixed dosing regimens. Additionally, DOACs have rapid onset of action and shorter half-lives compared to VKAs. DOACs are metabolised through multiple pathways, including hepatic enzymes, such as P-glycoprotein and CYP enzymes, and renal excretion. Consequently, they are more dependent on renal function for clearance, which dose adjustments are required in patients with renal impairment.

To date, a number of non-randomised studies have evaluated the comparative efficacy and safety of DOACs versus warfarin (Supplementary Table 6). Consequently, current evidence does not conclusively indicate which DOAC is most effective for managing NVAF in CKD patients. Our review identified three prospective [2-4] and fifteen retrospective observational studies [5-19], six of which undertook propensity-matched analyses (Supplementary Table 6) [5-9, 19]. Most of these studies (n=14) compared the efficacy and safety outcomes between DOACs and VKAs. Some studies also explored the association between varying doses of DOACs (apixaban and rivaroxaban) and clinical outcomes. It is important to note that many studies grouped patient cohorts with CKD stages 4 and 5 in their study design, which limits the ability to perform subgroup analyses specific to CKD stage 4. One multicentre retrospective cohort study utilised Cox proportional hazards models with propensity score matching to assess the efficacy and safety of rivaroxaban versus warfarin [20]. In patients with CKD stage 4, rivaroxaban was associated with a 22% lower risk of TIA, stroke, and death (HR 0.78; 95% CI 0.62-0.99) compared to warfarin, with no significant difference in major bleeding risk (HR 0.63; 95% CI 0.37-1.09) [20].

Collectively, the literature identified in our review suggests that DOACs and VKAs demonstrate comparable outcomes for TIA, stroke and thromboembolic risk reduction, with marginal trends favouring DOACs in two studies [20, 21]. However, many studies report no statistically significant difference. While all-cause mortality was not reported in several studies, DOACs show a consistent trend toward lower all-cause mortality compared to VKAs [5, 20]. In terms of bleeding risk, the findings are mixed, with some studies favouring DOACs and others reporting no significant difference compared to VKAs. It is important to recognise that variability in results is likely due to differences in study populations and methodologies. Therefore, high-quality studies are needed to confirm these findings to allow for more definitive guidance in this area.

Apixaban is less dependent on renal clearance compared to other DOACs, making it a favourable option in patients with renal impairment when warfarin is not a feasible choice of anticoagulation. However, dosing uncertainties exist and a study by Xu et al in severe chronic kidney disease found that the apixaban 5mg twice daily versus 2.5mg twice daily had no difference in SSE but a higher risk of bleeding and the authors suggest that the European dosing is supported over the FDA dosing [20].

The 2023 ACC/AHA/ACCP/HRS clinical practice guidelines recommend either warfarin or a licensed dose of DOAC as appropriate options for managing NVAF in patients with stage 4 CKD [21]. In contrast, the 2024 ESC guidelines do not make specific recommendations for DOAC use in advanced CKD, but emphasise that DOAC dosing should align with current EU licensing recommendations [22]. A recent UK-based Delphi study revealed that clinicians in nephrology and haematology show a modest preference for DOACs, mainly apixaban, over VKAs [8]. However, this preference was marginal, suggesting no substantial difference in decision-making when choosing between the two

classes of oral anticoagulation therapy. The choice of oral anticoagulant therapy should be individualised, taking into account patient-specific characteristics and factors that may influence medication adherence.

CKD stage 5

The literature on efficacy and safety outcomes of oral anticoagulation for non-dialysis dependent stage 5 CKD is limited to a small number of studies (n=13) with significant heterogeneity, rendering the evidence base for anticoagulation options in this patient cohort inconclusive (Supplementary Table 7) [5, 8-11, 13, 15, 16, 18-20, 24-28]. Most data are derived from retrospective observational studies, with only one prospective cohort study identified. Propensity score matching was employed in the study design in eight studies included in this review [5, 6, 8, 9, 19, 20, 25, 26].

These studies primarily focused on SSE as efficacy outcomes, with major bleeding designated as the main safety endpoint. Data on clinically relevant non-major bleeding (CRNM) and minor bleeding events were scarce, and only four studies reported results on all-cause mortality [5, 20, 24, 26].

Key findings from Xu et al revealed that standard dose of apixaban (5mg BD) was associated with a higher risk of bleeding events (sHR 1.63; 95% CI 1.04-2.54) compared to a reduced dose of 2.5mg BD, supporting the current licensed recommendation for reduced dosing in patients with severe renal impairment down to CrCl of 15m/min [20]. Notably, no significant differences were observed in the risk of stroke, systemic embolism, or death. A prospective cohort study assessed the clinical outcomes for all DOACs but the sample size was too small to achieve adequate statistical power and clinically meaningful results [24].

A recurring limitation across these studies was the inclusion of patients with a wide range of eGFR values, often combining CKD stages 4 and 5. This aggregation obscured the ability to accurately assess the effects of each oral anticoagulant specifically in patients with non-dialysis dependent CKD stage 5.

The current license of apixaban, edoxaban and rivaroxaban permits their use down to a CrCl of 15ml/min with appropriate dose adjustments. However, the evidence supporting the safety and efficacy of these dosing strategies in this population remains underexplored.

Dialysis

Prevalent dialysis cohorts have the most substantial amount of prospective evidence available [24, 29-31] (Supplementary Table 8). To date, three RCTs, including AXADIA-AFNET 8, RENAL-AF and Valkyrie, have examined the efficacy and safety of DOACs in individuals undergoing maintenance HD [32-34]. Key characteristics and outcomes of these RCTs are summarised in Supplementary Table 9. It is important to note the existing RCT evidence is limited to the HD population, with the use of DOACs in PD being assessed mainly through observational studies. Due to insufficient statistical power, the results from RENAL-AF cannot be used to draw definitive conclusions.

AXADIA-AFNET 8 is the most recent RCT that evaluated the efficacy and safety of apixaban at a dose of 2.5mg BD in dialysis patients compared to VKA [28]. The study used the Cox proportional hazard model and found no difference in the primary composite efficacy outcome (composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism)

(HR 0.764; 95% CI 0.343-1.700) between treatment groups. There was also no difference in the composite safety outcome defined by a first event of major bleeding, clinically relevant nonmajor bleeding, or all-cause death (HR 0.93; 95% CI 0.53-1.65) between apixaban and VKA.

Despite emerging evidence, there remains a lack of compelling evidence to guide the optimal dosing of apixaban in dialysis patients. The US retrospective cohort study by Siontis et al involving 25,523 patients reported no difference in SSE between apixaban and warfarin (HR 0.88; 95% CI 0.69-1.12) [35]. Notably, apixaban significantly reduced major bleeding risk (HR 0.72; 95% CI 0.59-0.87). Sensitivity analyses indicated that apixaban 5mg twice daily (BD) significantly reduced the risks of SSE (HR 0.61; 95% CI 0.37-0.98) and mortality (HR 0.64; 95% CI 0.45-0.92) compared to apixaban 2.5mg BD. The conflicting findings underscore the need for further research to determine optimal apixaban dosing for NVAF management in the dialysis population.

The Valkyrie study was the first RCT to assess rivaroxaban in HD patients [34]. The reduced rivaroxaban dose at 10mg OD was associated with a significantly reduced risk of fatal and non-fatal stroke compared to VKAs (HR 0.41; 95% CI 0.25-0.68). Furthermore, the safety endpoints, such as major bleeding, were reduced in the rivaroxaban group compared to VKA (HR 0.39; 95% CI 0.17-0.90). Despite these promising results, the small sample size of 132 participants limits generalisability and statistical robustness of these results.

In addition to SAFE-D (NCT03987711), APIDP2 is a French randomised open-label study (NCT06045858) currently under recruitment. It will be the first RCT that evaluates the comparative efficacy and safety of apixaban at reduced dose of 2.5mg BD and warfarin in PD patients [36].

Apixaban is currently the only DOAC that has been approved for use in dialysis by the United States Food and Drug Administration (FDA). In contrast, apixaban remains unlicensed for use in patients with dialysis-dependent CKD in the UK and Europe. While the current ESC guidelines do not provide any specific recommendations for DOAC use in the dialysis population, the 2023 ACC clinical practice guidelines recommend treatment with either warfarin or an evidence-based dosing of apixaban is appropriate for managing NVAF in patients with end-stage renal disease, including those on dialysis [21]. Clinicians should consider risk stratification and the choice between DOACs and VKAs in the context of labile INR, the risk of calciphylaxis, and the ease of access to INR monitoring required for VKA therapy. Instances where VKA use would be contraindicated include VKA-induced skin necrosis and calciphylaxis.

Dialysis circuit anticoagulation in people therapeutically anticoagulated

There are concerns that for those fully anticoagulated, additional anticoagulation for the dialysis circuit may pose an additional haemorrhagic risk. It is unclear whether there is a need for additional anticoagulation in patients on long-term oral anticoagulation to prevent circuit clotting. One small study suggested that haemodialysis without additional anticoagulation is possible in patients taking oral anticoagulation [37]. From the Delphi consensus we therefore suggest that for haemodialysis patients therapeutically anticoagulated they should initially undergo dialysis without additional dialysis circuit anticoagulation.

Calciphylaxis

When prescribing VKAs consideration should be given to the rare life-threatening condition calciphylaxis. Calciphylaxis is a syndrome of vascular calcification where there is occlusion of microvessels that results in extremely painful, ischemic skin lesions [38]. Calciphylaxis typically affects people with end-stage kidney disease (ESKD). However, warfarin increases the risk of calciphylaxis with approximately 50% of those with ESKD and calciphylaxis taking on warfarin [39, 40]. Warfarin has been shown to increase mortality risk in those with calciphylaxis [40]. VKAs are contraindicated in patients with calciphylaxis and alternative options should be discussed with the patient.

Patients on the deceased-donor kidney transplant waiting list

For patients on the deceased donor transplant waiting list having a readily reversible agent is preferred as urgent anticoagulation reversal is required before surgery [41]. Delaying transplant surgery to allow for DOAC clearance is not possible and this is the reason many transplant centres opt for VKAs [41]. There is a dearth of data on managing use of DOACs around the time of a deceased donor transplant. Therefore, we suggest that VKAs remain the preferred option when the patient is on the kidney transplant waiting list.

There is promise in the use of urine dipstick tests to detect clinically relevant DOAC levels [42]. This test can provide a rapid assessment of whether DOAC is present to guide clinical management such as procedures [42]. However, at present the use of this assay in those with impaired renal function may produce false negative results and further work is needed to make an assay suitable for those with advanced kidney disease. The ideal solution would be a point of care blood test which could be used in those patients who are also anuric, but this is yet to be developed.

Practice recommendations

We suggest a shared decision-making approach with appropriate counselling on risks and benefits of different treatment options, see appendix 1. **2C**

For patients on the deceased-donor transplant waiting list commencing anticoagulation we suggest this is with a VKA. **2D**

In CKD stage 4 (eGFR 15-<30) for NVAF thromboprophylaxis we recommend offering either**:**

- Apixaban 2.5mg twice daily
- Edoxaban 30mg daily
- Rivaroxaban 15mg daily
- VKA **2B**

In CKD stage 5 (eGFR<15 not on dialysis) for NVAF thromboprophylaxis we suggest offering either:

- Apixaban 2.5mg twice daily
- VKA **2C**

In Dialysis (haemodialysis/peritoneal dialysis) for NVAF thromboprophylaxis we suggest offering either:

- Apixaban 2.5mg twice daily
- VKA **2C**

Patients on haemodialysis who are therapeutically anticoagulated should initially undergo dialysis without additional dialysis circuit anticoagulation. **2D**

Research recommendations

- Trials to assess the safety and efficacy outcomes of apixaban versus VKAs in patients with advanced kidney disease.
- Trials to assess the safety and efficacy outcomes of rivaroxaban versus VKAs in patients with advanced kidney disease.
- Trials to assess DOAC dosing in advanced CKD assessing safety and efficacy outcomes.

References

1. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;109(4):569-79.
2. Kreutz R, Deray G, Floege J, Gwechenberger M, Hahn K, Luft AR, et al. Rivaroxaban vs Vitamin K Antagonist in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease. JACC Adv. 2024;3(2):100813.
3. Chantrarat T, Krittayaphong R. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and chronic kidney disease in Asian Population, Data from the COOL-AF Thailand registry. Int J Cardiol. 2021;323:90-9.
4. Heleniak Z, Papuga-Szela E, Krzysztof P, Anetta U. Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Chronic Kidney Disease Stage G4: A Single-Center Experience. J Cardiovasc Pharmacol. 2020;76(6):671-7.
5. Ha JT, Scaria A, Andrade J, Badve SV, Birks P, Bota SE, et al. Safety and Effectiveness of Rivaroxaban Versus Warfarin Across GFR Levels in Atrial Fibrillation: A Population-Based Study in Australia and Canada. Kidney Med. 2023;5(7):100675.
6. Lin Y, Chao TF, Tsai ML, Tseng CJ, Wang TH, Chang CH, et al. Cardiovascular and renal outcomes in patients with atrial fibrillation and stage 4-5 chronic kidney disease receiving direct oral anticoagulants: a multicenter retrospective cohort study. J Thromb Thrombolysis. 2024;57(1):89-100.
7. Koretsune Y, Hoshino H, Matsuo Y, Ibuki T, Morimoto T. Comparative Safety and Effectiveness of Apixaban vs. Warfarin in Oral Anticoagulant-Naïve Japanese Patients With Non-Valvular Atrial Fibrillation - A Retrospective Chart Review Study. Circ J. 2022;86(2):213-21.
8. Fu CM, Li LC, Lee YT, Wang SW, Hsu CN. Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease. Front Cardiovasc Med. 2021;8:752468.
9. Weir MR, Ashton V, Moore KT, Shrivastava S, Peterson ED, Ammann EM. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease. Am Heart J. 2020;223:3-11.
10. Hsu CC, Chen CC, Chou CY, Chen KH, Wang SF, Chang SL, et al. Effectiveness and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation and advanced kidney disease. J Thromb Thrombolysis. 2023;56(4):518-28.

11. Kee YK, Jeon HJ, Oh J, Yoo TH, Kang D, Lee J, et al. Direct oral anti-Xa anticoagulants versus warfarin in newly diagnosed atrial fibrillation and CKD: the Korean National Health Insurance Data. Front Med (Lausanne). 2023;10:1212816.
12. Vaitsiakhovich T, Coleman CI, Kleinjung F, Vardar B, Schaefer B. Worsening of kidney function in patients with atrial fibrillation and chronic kidney disease: evidence from the real-world CALLIPER study. Curr Med Res Opin. 2022;38(6):937-45.
13. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Efficacy and safety of warfarin in patients with non-valvular atrial fibrillation and CKD G3-G5D. Clin Kidney J. 2022;15(6):1169-78.
14. Wetmore JB, Weinhandl ED, Yan H, Reyes JL, Herzog CA, Roetker NS. Apixaban Dosing Patterns Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation Receiving Dialysis: A Retrospective Cohort Study. Am J Kidney Dis. 2022;80(5):569-79.e1.
15. Chang SH, Wu CV, Yeh YH, Kuo CF, Chen YL, Wen MS, et al. Efficacy and Safety of Oral Anticoagulants in Patients With Atrial Fibrillation and Stages 4 or 5 Chronic Kidney Disease. Am J Med. 2019;132(11):1335-43.e6.
16. Coleman CI, Kreutz R, Sood NA, Bunz TJ, Eriksson D, Meinecke AK, et al. Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis. Am J Med. 2019;132(9):1078-83.
17. Di Lullo L, Tripepi G, Ronco C, De Pascalis A, Barbera V, Granata A, et al. Safety and effectiveness of rivaroxaban and warfarin in moderate-to-advanced CKD: real world data. J Nephrol. 2018;31(5):751-6.
18. Lai HM, Aronow WS, Kalen P, Adapa S, Patel K, Goel A, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. Int J Nephrol Renovasc Dis. 2009;2:33-7.
19. Fu EL, Desai RJ, Paik JM, Kim DH, Zhang Y, Mastrorilli JM, et al. Comparative Safety and Effectiveness of Warfarin or Rivaroxaban Versus Apixaban in Patients With Advanced CKD and Atrial Fibrillation: Nationwide US Cohort Study. Am J Kidney Dis. 2024;83(3):293-305.e1.
20. Xu Y, Chang AR, Inker LA, McAdams-DeMarco M, Grams ME, Shin JI. Associations of Apixaban Dose With Safety and Effectiveness Outcomes in Patients With Atrial Fibrillation and Severe Chronic Kidney Disease. Circulation. 2023;148(19):1445-54.
21. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2024;83(1):109-279.
22. Van Gelder I, Rienstra M, Bunting K, Casado-Arroyo R, Caso V, Crijns H, et al. 2024 ESC Guidelines for the management of atrial fibrillation. European Heart Journal. 2024;45(36):3314-414.
23. Parker K, Choudhuri S, Lewis P, Thachil J, Mitra S. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. BMC Nephrol. 2023;24(1):9.
24. Park H, Yu HT, Kim TH, Park J, Park JK, Kang KW, et al. Oral Anticoagulation Therapy in Atrial Fibrillation Patients with Advanced Chronic Kidney Disease: CODE-AF Registry. Yonsei Med J. 2023;64(1):18-24.
25. Sy J, Wenziger C, Marroquin M, Kalantar-Zadeh K, Kovesdy C, Streja E. Warfarin Use, Stroke, and Bleeding Risk among Pre-Existing Atrial Fibrillation US Veterans Transitioning to Dialysis. Nephron. 2022;146(4):360-8.
26. Jun M, James MT, Ma Z, Zhang J, Tonelli M, McAlister FA, et al. Warfarin Initiation, Atrial Fibrillation, and Kidney Function: Comparative Effectiveness and Safety

of Warfarin in Older Adults With Newly Diagnosed Atrial Fibrillation. Am J Kidney Dis. 2017;69(6):734-43.
27. Lin YC, Chen BL, Shih CM, Lin FY, Chen CW, Hsu CY, et al. Effectiveness and safety of rivaroxaban versus warfarin in Taiwanese patients with end-stage renal disease and nonvalvular atrial fibrillation: A real-world nationwide cohort study. PLoS One. 2021;16(4):e0249940.
28. Wetmore JB, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-Acting Oral Anticoagulants Versus Warfarin in Medicare Patients With Chronic Kidney Disease and Atrial Fibrillation. Stroke. 2020;51(8):2364-73.
29. Wakasugi M, Kazama JJ, Tokumoto A, Suzuki K, Kageyama S, Ohya K, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. Clin Exp Nephrol. 2014;18(4):662-9.
30. Königsbrügge O, Posch F, Antlanger M, Kovarik J, Klauser-Braun R, Kletzmayr J, et al. Prevalence of Atrial Fibrillation and Antithrombotic Therapy in Hemodialysis Patients: Cross-Sectional Results of the Vienna InVestigation of AtriaL Fibrillation and Thromboembolism in Patients on HemoDIalysis (VIVALDI). PLoS One. 2017;12(1):e0169400.
31. Genovesi S, Rebora P, Gallieni M, Stella A, Badiali F, Conte F, et al. Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study. J Nephrol. 2017;30(4):573-81.
32. Reinecke H, Engelbertz C, Bauersachs R, Breithardt G, Echterhoff HH, Gerß J, et al. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. Circulation. 2023;147(4):296-309.
33. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. Circulation. 2022;146(23):1735-45.
34. De Vriese AS, Caluwé R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. J Am Soc Nephrol. 2020;31(1):186-96.
35. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation. 2018;138(15):1519-29.
36. Ficheux M, Peyro-Saint-Paul L, Balayn D, Lecrux B, Brossier M, Morin A, et al. Safety and efficacy of apixaban versus warfarin in peritoneal dialysis patients with non-valvular atrial fibrillation: protocol for a prospective, randomised, open-label, blinded endpoint trial (APIDP2). BMJ Open. 2024;14(9):e089353.
37. Krummel T, Scheidt E, Borni-Duval C, Bazin D, Lefebvre F, Nguyen P, et al. Haemodialysis in patients treated with oral anticoagulant: should we heparinize? Nephrol Dial Transplant. 2014;29(4):906-13.
38. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med. 2018;379(4):399-400.
39. Brandenburg VM, Kramann R, Rothe H, Kaesler N, Korbiel J, Specht P, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. Nephrol Dial Transplant. 2017;32(1):126-32.
40. Santos PW, He J, Tuffaha A, Wetmore JB. Clinical characteristics and risk factors associated with mortality in calcific uremic arteriolopathy. Int Urol Nephrol. 2017;49(12):2247-56.
41. Rimsans J, Sylvester K, Kim M, Connors JM, Gabardi S. A Review of Direct-acting Oral Anticoagulants and Their Use in Solid Organ Transplantation. Transplantation. 2022;106(11):2143-54.

42. Harenberg J, Gosselin RC, Cuker A, Becattini C, Pabinger I, Poli S, et al. Algorithm for Rapid Exclusion of Clinically Relevant Plasma Levels of Direct Oral Anticoagulants in Patients Using the DOAC Dipstick: An Expert Consensus Paper. Thromb Haemost. 2024 Aug;124(8):770-777.

Section 5: Monitoring and follow up

Rationale

Warfarin (and other vitamin K antagonists)

National and International guidance recommend that VKA therapy is monitored using the international normalised ratio (INR) with a target range of 2-3 when used for AF [1-3]. The frequency of INR monitoring and dosage adjustments are subject to local variation, but a typical protocol in the UK recommends that when warfarin is initiated that daily or alternate day monitoring should be undertaken until two consecutive INR values are in range. This should then reduce to once or twice weekly measurements until two consecutive INR values are in range, thereafter less frequent measurements can be undertaken (up to a maximum of 12 weekly) depending on the stability of the INR [4]. More frequent monitoring (e.g. every 1-2 weeks) is recommended for patients with renal impairment [4], however, no definitive guidance was identified for this population and none of the studies identified evaluated this aspect of care. Our recommendation is therefore based on the available guidance for the general population.

INR monitoring can be done in different settings including general practice, specialised clinics, dialysis centres, or at home by the patient using point of care (POC) testing devices. The accuracy of the CoaguChek S device (Roche Diagnostics, Indianapolis, Indiana) has been tested against laboratory INR testing in a small cohort of 37 haemodialysis patients in the USA, this found a reasonable correlation between POC measurement and laboratory measurement with the POC measurement being within 0.2 of the laboratory measurement 67% and within 0.4 89% of the time [5].

In addition to regular INR monitoring, the National Institute for Health and Care Excellence (NICE) and European Society of Cardiology (ESC) recommend that overall anticoagulation control with warfarin be monitored using the Time in Therapeutic Range (TTR), calculated using a validated method of measurement as this higher TTR is associated with a lower risk of adverse outcomes in the general population [1,2]. However, targets vary with UK guidance suggesting a target of more than 65% [1] and European and American guidance more than 70% [2, 3].

The TTR for patients with severe to end-stage CKD, including those on dialysis has been evaluated in numerous studies. Patients with CKD or on dialysis frequently have suboptimal TTRs compared with the general population with estimates and TTR appears to worsen as renal function declines [6-9]. Most studies of patients with severe CKD and dialysis have reported suboptimal TTR ranging from 44% to 62% [6, 8-13]. . Studies from Sweden and the Netherlands, who have previously been shown to have good anticoagulation control in the general population, found TTRs of over 65% in patients with severe CKD and dialysis but these were lower than for those without CKD [6, 14, 15].

Low TTR has been associated with adverse clinical outcomes[6], low TTR alongside severe CKD can therefore significantly increase the risk of adverse events [16]. Patients with severe CKD and those on dialysis are significantly more likely to experience subtherapeutic and supratherapeutic INR levels, with a concurrent increase in the risk of ischaemic stroke, minor and major haemorrhage, and death compared to those with mild or moderate CKD [7, 8, 9, 16, 17]. Increasing TTR to ≥ 70% has been

associated with a significant reduction in risk of major bleeding and all-cause mortality in patients with severe CKD and those on dialysis and a trend towards a reduction in ischaemic stroke [7].

There is debate whether TTR is the most important factor when determining adequacy of anticoagulation in patients with severe CKD. A study from the Netherlands reported a TTR rate of 70% in patients with severe CKD, comparable to patients with moderate or without CKD [14]. However, even though TTR was acceptable, the rate of adverse events was still higher in patients with severe CKD. The authors found that INR variability was significantly higher in those with severe CKD compared with no or moderate CKD and analyses suggested that this may mediate the already increased risk of cardiovascular events and major bleeding in this group [18]. A further study in Italy suggested that increasing INR variability may have a more significant impact on mortality and bleeding than TTR [13]. For each unit increase in the standard deviation of INR the hazard of all-cause mortality rose by 67% (HR 1.67, 95% CI 1.12-2.49), whereas for TTR >65% compared with less than 65% there was no significant effect on mortality (HR 0.77, 95% CI 0.42-1.4) [13]. A TTR ≥ 65% was associated with a lower risk of recurrent bleeds (HR 0.35, 95% CI 0.15-0.8), but standard deviation of INR may be a stronger predictor per one unit increase (HR 2.44, 95% CI 1.43-4.15) [13].

There is insufficient evidence to ascertain whether the benefits of higher TTR are maintained in patients with severe CKD, but aiming for a higher TTR would not appear to cause harm so we recommend to follow the guidance issued by NICE [1]. Poor TTR should be considered as part of shared decision making with patients about whether there should be consideration of switching to a DOAC.

DOACs

Studies have shown prolongation of half-life and increased drug exposure (represented by concentration area under curve (AUC)) for all DOACs, in patients with renal impairment, including patients requiring dialysis treatment.

There have been some analyses of the relationship between drug levels and measures of coagulation in the CKD population.

Apixaban has been the most frequently studied DOAC to-date. Studies have analysed apixaban pharmacokinetics, after a single dose or at steady state in patients with CKD, including those requiring HD treatment. Analysis of participants who had CrCl 25-30 ml/min in the ARISTOTLE trial showed that the median AUC for apixaban concentrations increased with lower CrCl , but the range of values was not different to patients with relatively preserved renal function (CrCl >30ml/min) [19]. A further study in patients with CKD stage 1-4 found a negative correlation between both peak and trough apixaban levels and CrCl (apixaban levels rising as CrCl decreased), when apixaban was given at 5mg BD dose [20]. The relationship was less strong when given at 2.5mg BD dose [21]. Real-world data from hospitalized patients, including both CKD and non-CKD, with median CrCl 57.2 ml/min, suggests that Creatinine clearance is a significant determinant of apixaban clearance [21]. Investigation of steady-state apixaban pharmacokinetics in haemodialysis patients have found no difference in pharmacokinetic measurements (including trough (Cmin) and peak (Cmax) apixaban levels and AUC) between patients receiving haemodialysis treatment and patients with non-dialysis CKD (CrCl 15-60) when given the same dose [22, 23]. Together, these studies show an effect of reduced

kidney function on apixaban concentrations, but no difference between non-dialysis CKD and HD treated patients.

Several studies have investigated the effect of dialysis treatment on apixaban concentrations. Whilst single dose studies suggest an impact in timing pre-, post dialysis this effect is not seen in patients once at steady state (22, 24, 25. 26). In patients receiving PD, the AUC of Apixaban concentrations appears to be increased, compared with both HD patients and healthy subjects, after either 1 week of 2.5mg BD, or a single dose of 5mg [27, 28].

Two studies of Rivaroxaban in HD subjects have found similar Cmax, but increased AUC compared with healthy subjects. Neither study found a difference between pre- or post-dialysis dosing on rivaroxaban levels [29, 30].

Edoxaban concentrations were compared between those with CrCl 15- 29ml/min taking 15mg daily and CrCl >50ml/min taking either 30mg or 60mg [31]. There is no available AUC data, but trough levels in patients with reduced renal function appear to be similar to patients with CrCl > 50 ml/min taking 60mg.

Critically, there is little evidence in the CKD population to suggest a relationship between pharmacokinetic measures of DOACs and clinical outcomes. This relationship has been examined in just three studies. In a prospective observational cohort of patients with CKD1-4, the mean trough, but not peak, Apixaban level was significantly higher in those who had bleeding episodes, compared to those without bleeding episodes; there was no association between peak or trough levels and ischaemic events [20]. In contrast, in the RENAL-AF randomised trial of Apixaban, there were no differences in pharmacokinetic values between those with bleeding events and those without, including Cmax, Cmin and AUC0-12 [23].

In summary, pharmacokinetic studies of DOACs, both at steady state and after single doses, suggest that drug exposure, as represented by AUC, is likely to be increased in patients with CKD, either non-dialysis or requiring dialysis, but the effect is mitigated by dose adjustment according to licensed guidelines. Studies consistently show that there is no effect of renal function on peak drug levels. Despite some effect of haemodialysis treatment on drug levels, there does not appear to be a marked difference in drug exposure between non-dialysis CKD and those on HD treatment; PD treatment appears to be associated with higher drug exposure. There is a paucity of evidence linking drug levels and pharmacokinetics to clinical endpoints. Routine monitoring of DOAC exposure is not recommended in the licensing for any of these medications [32-34].

Standard monitoring of DOACs such as liver function, full blood count and renal function should be monitored as per frequency defined in the manufacturer's information [32-34] and European Heart and Rhythm Association (EHRA) guideline [36]

Practice recommendations

- We recommend that VKA therapy should be monitored using the international normalised ratio (INR). **1A**
- Frequency of monitoring and dose adjustments should be defined in local protocols

- We recommend that anticoagulation control with warfarin should be assessed using Time in Therapeutic range (TTR), aiming for TTR ≥65%. **1B**
- For patients with advanced kidney disease including those on dialysis discuss options of where INR monitoring can take place and allow patient to choose if there are multiple options **2D**
- Anticoagulation with VKA's should be reassessed where TTR is less than 65%. This assessment should consider adherence, cognitive function, illness, interacting medications, and lifestyle factors. **2C**
- We suggest that monitoring of peak and trough DOAC levels is not necessary in advanced CKD unless an additional reason to monitor is present i.e. potential drug-drug interaction. **2C**

Research recommendations

- Evaluate whether methods to combine TTR and INR variability are feasible in practice and whether these measures can be used concurrently to improve safety and effectiveness outcomes with VKAs.
- Further research is required on the utility of monitoring DOAC levels, both peak and trough levels should be considered and results correlated with hard clinical outcomes.

References

1. National Institute for Health and Care Excellence (NICE). NICE guideline [NG196}. Atrial fibrillation: diagnosis and management 2021 [cited 2024 30 May]. Available from: https://www.nice.org.uk/guidance/ng196/chapter/Recommendations#stroke-prevention.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2021;42(5):373-498.
3. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(1).
4. National Institute for Health and Care Excellence (NICE). Clinical Knowledge Summary - Scenario: Warfarin 2024 [cited 2024 30 May]. Available from: https://cks.nice.org.uk/topics/anticoagulation-oral/management/warfarin/.
5. Hoel RW, Albright RC, Beyer LK, Santrach PJ, Magtibay DL, Everson SL, et al. Correlation of point-of-care International Normalized Ratio to laboratory International Normalized Ratio in hemodialysis patients taking warfarin. Clin J Am Soc Nephrol. 2009;4(1):99-104.
6. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. Am Heart J. 2015;170(1):141-8, 8.e1.
7. Szummer K, Gasparini A, Eliasson S, Ärnlöv J, Qureshi AR, Bárány P, et al. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. J Am Heart Assoc. 2017;6(3).

8. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Warfarin treatment quality and outcomes in patients with non-valvular atrial fibrillation and CKD G3-G5D. Thromb Res. 2023;229:131-8.
9. Yang F, Hellyer JA, Than C, Ullal AJ, Kaiser DW, Heidenreich PA, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. Heart. 2017;103(11):818-26.
10. Lamontagne S, Basein T, Chang B, Mallela L. A hemodialysis cohort study of protocol-based anticoagulation management. BMC Res Notes. 2017;10(1):66.
11. Niznik RS, Hoel RW, Vaughan LE, Majorowicz RR, Albright RC, Jr. Time in Therapeutic Range for Dialysis Patients on Warfarin: Determination and the Effect of Dietary Intervention. Mayo Clin Proc. 2020;95(6):1206-11.
12. Praehauser C, Grandjean R, Steiger J, Mayr M. Cohort study on the quality of oral anticoagulation therapy in chronic haemodialysis patients treated with phenprocoumon. Swiss Med Wkly. 2013;143:w13730.
13. Rebora P, Moia M, Carpenedo M, Valsecchi MG, Genovesi S. Best quality indicator of vitamin K antagonist therapy to predict mortality and bleeding in haemodialysis patients with atrial fibrillation. Blood Transfus. 2021;19(6):487-94.
14. Kooiman J, Van Rein N, Spaans B, Van Beers KAJ, Bank JR, Van De Peppel WR, et al. Efficacy and safety of vitamin K-antagonists (VKA) for atrial fibrillation in non-dialysis dependent chronic kidney disease. PLoS ONE. 2014;9(5):e94420.
15. Batra G, Modica A, Renlund H, Larsson A, Christersson C, Held C. Oral anticoagulants, time in therapeutic range and renal function over time in real-life patients with atrial fibrillation and chronic kidney disease. Open Heart. 2022;9(2).
16. Chantrarat T, Krittayaphong R. The Clinical Outcomes of Different eGFR Strata and Time in Therapeutic Range in Atrial Fibrillation Patients with Chronic Kidney Disease: A Nationwide Cohort Study. Current Problems in Cardiology. 2021;46(9):100838.
17. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009;20(4):912-21.
18. Kooiman J, van der Hulle T, Maas H, Wiebe S, Formella S, Clemens A, et al. Pharmacokinetics and Pharmacodynamics of Dabigatran 75 mg b.i.d. in Patients With Severe Chronic Kidney Disease. J Am Coll Cardiol. 2016;67(20):2442-4.
19. Stanifer JW, Pokorney SD, Chertow GM, Hohnloser SH, Wojdyla DM, Garonzik S, et al. Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease. Circulation. 2020;141(17):1384-92.
20. Sin CF, Wong KP, Wong TF, Siu CW, Yap DYH. Plasma apixaban levels in Chinese patients with chronic kidney disease-Relationship with renal function and bleeding complications. Frontiers in Pharmacology. 2022;13:928401.
21. Gaspar F, Terrier J, Favre S, Gosselin P, Fontana P, Daali Y, et al. Population pharmacokinetics of apixaban in a real-life hospitalized population from the OptimAT study. CPT: Pharmacometrics and Systems Pharmacology. 2023;12(10):1541-52.
22. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. J Am Soc Nephrol. 2017;28(7):2241-8.
23. Pokorney SD, Chertow GM, Al-Khalidi HR, Gallup D, Dignacco P, Mussina K, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. Circulation. 2022;146(23):1735-45.
24. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56(5):628-36.

25. Van den Bosch I, Bouillon T, Verhamme P, Vanassche T, Jacquemin M, Coemans M, et al. Apixaban in patients on haemodialysis: a single-dose pharmacokinetics study. Nephrol Dial Transplant. 2021;36(5):884-9.
26. Poel T, de Rouw N, Péquériaux NCV, van de Kerkhof D, Windsant A, van Marum RJ, et al. Effect of conventional hemodialysis on the apixaban plasma concentration. Hemodial Int. 2024;28(1):72-6.
27. Fung WWS, Cheng PMS, Ng JKC, Chan GCK, Chow KM, Li PKT, et al. Pharmacokinetics of Apixaban Among Peritoneal Dialysis Patients. Kidney Medicine. 2023;5(8):100646.
28. Peyro-Saint-Paul L, Bechade C, Cesbron A, Debruyne D, Brionne M, Brucato S, et al. Effect of peritoneal dialysis in end-stage renal disease on apixaban pharmacokinetics. Nephrol Dial Transplant. 2023;38(8):1918-20.
29. Dias C, Moore KT, Murphy J, Ariyawansa J, Smith W, Mills RM, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis. Am J Nephrol. 2016;43(4):229-36.
30. De Vriese AS, Caluwé R, Bailleul E, De Bacquer D, Borrey D, Van Vlem B, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015;66(1):91-8.
31. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-Term Safety and Plasma Concentrations of Edoxaban in Japanese Patients With Non-Valvular Atrial Fibrillation and Severe Renal Impairment. Circ J. 2015;79(7):1486-95.
32. Bristol-Meyers Squibb-Pfizer. Eliquis 5 mg film-coated tablets. Electronic Medicines Compendium [Internet]. 2024 [cited 2024 30 May]. Available from: https://www.medicines.org.uk/emc/product/2878/smpc#gref.
33. Bayer plc. Xarelto 20mg film-coated tablets. Electronic Medicines Compendium. 2023 [cited 2024 30 May]. Available from: https://www.medicines.org.uk/emc/product/2793/smpc.
34. Boehringer Ingelheim Limited. Pradaxa 150 mg hard capsules. Electronic Medicines Compendium.lixiana 2024 [cited 2024 30 May]. Available from: https://www.medicines.org.uk/emc/product/4703/smpc#gref.
35. Daiichi Sankyo UK Limited. Lixiana 30mg Film-Coated Tablets. Electronic Medicines Compendium. 2024 [cited 2024 30 May]. Available from: https://www.medicines.org.uk/emc/product/6906/smpc.
36. Steffel J et al. European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation, EP Europace, Volume 23, Issue 10, October 2021, Pages 1612–1676

Section 6: Areas of interest

Section 6a. Left Atrial Appendage Occlusion (LAAO)

Overview

The left atrial appendage (LAA) is the primary source of thromboembolism in over 90% of patients with non-rheumatic atrial fibrillation [(1)]. In patients where formal anticoagulation is contraindicated there is the option of LAA closure through ligation, amputation, or occlusion (LAAO). This can be performed surgically or percutaneously. Following percutaneous closure of the LAA, a short course of anticoagulation with either a vitamin K antagonist or DOAC is recommended alongside aspirin for 45 days then dual antiplatelet therapy (DAPT) for a further 4.5 months [(2)]. If patients have an absolute contraindication to OAC, DAPT (Aspirin plus clopidogrel) is used for up to 6 months post procedure [(3)]. The FDA in 2022 released approval to expand the instructions for use labelling for the current-generation WATCHMAN FLX LAAO device to include a 45-day DAPT option as an alternative to 45-day OAC plus aspirin for post-procedural treatment of patients using data from the post approval NCDR-LAAO Registry [(4)].

Surgical Closure of the LAA

The atrial appendage can be ligated or amputated at the time of concomitant cardiac surgery for other indications. The procedure is performed routinely in patients with an indication for OAC, as an adjunct to OAC, in the hope of reducing future thromboembolic complications. Thoracoscopic approaches to specifically close the LAA exist although are rarely performed given availability of less invasive percutaneous approaches.

The LAAOS III trial, randomised individuals with AF undergoing cardiac surgery for another indication with a CHA_2DS_2-VASc score of at least two [(5)]. Participants were assigned to undergo (n=2379) or not undergo (n=2391) occlusion of the LAA during surgery. The primary outcome was the occurrence of SSE. Importantly all the participants were expected to receive usual care, including OAC, during follow-up. The study population, mean age 71 years, mean CHA_2DS_2-VASc score 4.2 and mean follow-up of 3.8 years. At 3-years, 76.8% of the participants continued to receive OAC. SSE occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% CI, 0.53 to 0.85; P = 0.001).

LAAOS III used a variety of techniques to close the LAA but did not report success rates of closure. Techniques of surgical closure can be incomplete with case series reporting rates of almost 40% [(6)]. Also, these patients have another primary indication for cardiac surgery and as such represent a limited cohort and one with significant associated cardiac conditions. To date there is limited data to support surgical LAAO without the use of anticoagulation.

Percutaneous LAAO Trials

The atrial appendage can be closed using a percutaneous plug e.g. WATCHMAN device, a Pacifier e.g. Amplatz or Amulet device or ligation technique e.g. LARIAT device [(8)]. The anatomy of the LAAO is heterogenous and detailed pre-procedure planning is vital prior to percutaneous closure involving a combination of trans-oesophageal echocardiography, cardiac CT and cardiac MRI. This is not

required for surgical approaches. The procedure is typically performed via the femoral venous route and requires a transseptal puncture to access the left atrium necessitating the use of heparin to avoid thrombosis of the catheters and occlusion device. The procedure is performed under conscious sedation or general anaesthetic and usually involves an overnight stay in hospital.

Studies, namely in a non-CKD population, have demonstrated percutaneous LAAO to be non-inferior to warfarin or DOACs for stroke and systemic embolism with a reduced risk of major bleeding [2, 8, 9, 10]. The two pivotal RCTs have focused on patients eligible for warfarin receiving the WATCHMAN device. As such it is the most implanted percutaneous LAAO device and has the most robust data to support its clinical use.

PROTECT-AF [2] is a multicentre, randomised, unblinded, non-inferiority study of 707 patients with NVAF and at least 1 additional stroke risk factor ($CHADS_2$ score ≥1) comparing the WATCHMAN device to warfarin (target INR 2-3). The device group received warfarin for 45 days after the implant with 4-year follow up. At a mean follow up the event rate (composite efficacy end point SSE, and cardiovascular / unexplained death) was 39/463 patients (8.4%) in the device group compared with 34/244 patients (13.9%) with warfarin (rate ratio, 0.60; 95% confidence interval, 0.41-1.05), meeting prespecified criteria for both noninferiority and superiority.

PREVAIL [8] was a follow up RCT that compared the WATCHMAN device with warfarin. Patients with NVAF who had a $CHADS_2$ score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned to undergo LAAO and subsequent discontinuation of warfarin (intervention group, n=269) or receive chronic warfarin therapy (control group, n=138). At 18 months percutaneous LAAO did not achieve non inferiority for the primary composite efficacy endpoint (composite of SSE and cardiovascular/unexplained death). The study had lower than expected event rates limiting statistical power. When compared in a meta-analysis the combined 5-year outcome data of PROTECT AF and PREVAIL demonstrates that the WATCHMAN device is non-inferior to warfarin for the composite of stroke, systemic embolism, and cardiovascular/unexplained death.

PRAGUE-17 [10] a multicentre, randomised, non-inferiority trial comparing percutaneous LAAO (n=201,) with DOACs (N=201) in patients with NVAF. Patients needed a history of bleeding requiring intervention or hospitalisation, a prior cardioembolic event while taking an OAC, and/or a CHA_2DS_2-VASc of ≥3 and HAS-BLED of >2. The primary composite outcome was SSE, cardiovascular death, major or non-major clinically relevant bleeding, or procedure-/ device-related complications. At a median 19.9 months of follow-up, the annual rates of the primary outcome were 10.99% with LAAO and 13.42% with DOAC (sub distribution hazard ratio [sHR]: 0.84; 95% CI: 0.53-1.31; p=0.44;) meeting non inferiority criteria. Device selection was at the discretion of the implanting centre (Amulet device 61.3%, WATCHMAN/WATCHMAN-FLX 38.7%) and following LAAO patients received 3 months of DAPT, in patients with a very high thrombotic risk, alternative regimens included DOAC substitution for DAPT for up to 3 months or DOACs for 6 weeks followed by DAPT for 6 weeks.

As the analysed RCTs have primarily included patients eligible for OAC, their results must be interpreted with caution in the wider AF population. Evidence for the safety and efficacy of percutaneous LAAO in patients unable to take OAC is only in the form of registries and case series to date.

Data specifically for LAAO in patients with CKD is scarce. The largest, real-world, multicentre cohort of LAAO patients categorised based on baseline kidney function included over 2100 patients receiving the WATCHMAN device. Of these 239 had CKD stage 4 or stage 5, 170 and 69 respectively. The primary endpoint included cardiovascular (CV) mortality, thromboembolism, and major bleeding. Procedural duration increased in parallel with CKD severity although procedural success and acute complication rates were unrelated to baseline CKD status. Post-implant antithrombotic regiment and follow-up strategies were left to each operator's preference. The incidence of the primary endpoint at 1 year and 2 years significantly increased with worsening CKD, 2-year cumulative incidence: 14.1 (CKD stage 1 and 2) vs. 18.2 (CKD 3) vs. 24.7 (CKD 4) vs. 32.7 (CKD 5). The relative risk reduction in the incidence of thromboembolism and major bleeding was consistent across CKD groups [11].

There remains a strong need for a formal RCT in this group. The LAA-KIDNEY trial (NCT05204212) is the first RCT to compare LAAC (Amplatzer Cardiac Plug and/or Amulet) with best medical therapy (including VKA, DOACs, antiplatelet agents or no anticoagulation) in patients with advanced CKD (eGFR <15 ml/min/1.73 m2) and NVAF with a high risk of stroke and bleeding. It is hoped that this study will achieve better recruitment than previous similar RCTs (Watch-AFIB (NCT02039167) and STOP-HARM (NCT02885545)) which unfortunately were terminated early due to slow enrollment.

Guidelines

In 2010, NICE made the following recommendations, for percutaneous LAA closure [12].

Current evidence suggests that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with NVAF. With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent, and audit.

Patient selection should be carried out by a multidisciplinary team including a cardiologist and other appropriate clinicians experienced in the management of patients with AF at risk of stroke.

Since publication, several critical changes to the commissioning and delivery of this service have occurred [13, 14]. In 2018, NHS England decided to support commissioning of LAAO in selected patients with NVAF and high thromboembolic risk, defined as a CHA_2DS_2-VASc≥2, and where there is a physician-assessed contraindication to OAC. All procedures undertaken must be recorded on a national Left Atrial Appendage Occlusion Registry [15].

The 2021 NICE guideline update "Atrial fibrillation diagnosis and treatment" reiterates the recommendation to not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated [16]. A consensus statement from the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions published in 2020 states that AF patients with CHA_2DS_2-VASc score ≥2 (3 in females) who have absolute contraindications for long-term OAC may be considered for LAAO if a minimum period (2-4 weeks) of a single antiaggregant can be given, and for those who are unwilling to take OAC after receiving personal and detailed advice that according to current evidence long-term OAC treatment is the preferred prophylactic strategy [7]. The 2023 American guidelines state in patients with AF with a

moderate to high-risk of stroke (CHA_2DS_2-VASc score ≥2), and a contraindication to long-term OAC percutaneous LAAO is reasonable 2a(B) indication [17].

Unresolved Concerns

Whilst the LAA is the primary source of thrombus formation in patients with non-rheumatic AF, over 10% of thrombi are not located within the LAA and as such occlusion will not eliminate the risk [1]. Furthermore, closure of LAA can be incomplete and a communication remain between the atrial appendage and the body of the LA. Assessment of closure remains controversial as does quantification of the residual leak and its relevance to ongoing thromboembolic risk [18]. The NCDR (National Cardiovascular Data Registry)-LAAO Registry, a post marketing surveillance registry used to evaluate patients within the USA who have undergone attempted LAAO with the WATCHMAN/WATCHMAN FLX devices reports successful percutaneous closure rates of <85% [19].

In patients with an indication for OAC it is not surprising to find the presence of left atrial thrombus when the LAA is imaged. In this scenario LAAO is contraindicated and if feasible a short term (<8 weeks) strategy of intense OAC is required before re-imaging to ensure resolution of the thrombus.

As with all new procedures with time and experience (operator and centre), procedural safety improves. Acute procedural complications are outside the scope of this document but may be significant. Longer term serious device complications are rare (<1%) and include device migration, erosion or embolisation plus the risk of endocarditis. Practical considerations with regards to patient selection and management of LAAO have recently been published [20].

Practice recommendations

In selected patients LAAO may be considered as an option. **2B**

References

1. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996 Feb;61(2):755-9.
2. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312:1988–1998.
3. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C, Swarup V, Whisenant B, Holmes D Jr Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2013;61(17):1790. Epub 2013 Feb 28.
4. Freeman, J, Varosy, P, Price, M. et al. The NCDR Left Atrial Appendage Occlusion Registry. J Am Coll Cardiol. 2020 Apr, 75 (13) 1503–1518.
5. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med 2021; 384:2081.
6. Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol. 2000;36(2):468.

7. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, Fauchier L, Betts TR, Lewalter T, Saw J, Tzikas A, Sternik L, Nietlispach F, Berti S, Sievert H, Bertog S, Meier B; ESC Scientific Document Group. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. Europace. 2020 Feb 1;22(2):184.
8. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64:1–12.
9. Doshi SK, Kar S, Sadhu A, Horton R,et al. Two-Year Outcomes With a Next-Generation Left Atrial Appendage Device: Final Results of the PINNACLE FLX Trial. Journal of the American Heart Association. 2023;12: e026295
10. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. J Am Coll Cardiol. 2020;75:3122–3135.
11. Rocca DGD, Magnocavallo M, Niekerk CJ van, Gilhofer T, Ha G, et al. Prognostic value of chronic kidney disease in patients undergoing left atrial appendage occlusion, EP Europace, Volume 25, Issue 11, November 2023, euad315, EP Europace, Volume 25, Issue 11, November 2023, euad315.
12. NICE guideline IPG349. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. 23 June 2010. www.nice.org.uk
13. Willits I, Keltie K, Linker N, de Belder M, Henderson R, et al. Left atrial appendage occlusion in the UK: prospective registry and data linkage to Hospital Episode Statistics, European Heart Journal - Quality of Care and Clinical Outcomes, Volume 7, Issue 5, November 2021, Pages 468–475, https://doi.org/10.1093/ehjqcco/qcab042
14. Ding WY, Gupta D. Percutaneous Left Atrial Appendage Occlusion: A View From the UK. Arrhythmia & Electrophysiology Review 2020;9(2):83–7.
15. National Cardiac Audit Programme. Left Atrial Appendage Occlusion (LAAO). Accessed via https://www.nicor.org.uk/national-cardiac-audit-programme/left-atrial-appendage-occlusion-laao
16. NICE guideline NG196. Atrial fibrillation: diagnosis and management NICE guideline [NG196]. Updated 30 June 2021. Accessed via https://www.nice.org.uk/guidance/ng196/chapter/Recommendations
17. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, et al; Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jan 2;149(1):e1-e156.
18. Alkhouli M, Du C, Killu A, Simard T, Noseworthy PA, et al. Clinical Impact of Residual Leaks Following Left Atrial Appendage Occlusion: Insights From the NCDR LAAO Registry. JACC Clin Electrophysiol 2022 Jun;8(6):766-778.
19. Ferro EG, Alkhouli M, Nair DG, Kapadia SR, Hsu JC, Gibson DN, Freeman JV, Price MJ, Roy K, Allocco DJ, Yeh RW, Piccini JP. Intracardiac vs Transesophageal Echocardiography for Left Atrial Appendage Occlusion With Watchman FLX in the U.S. JACC Clin Electrophysiol. 2023 Dec;9(12):2587-2599. doi: 10.1016/j.jacep.2023.08.004.
20. Potpara T, Grygier M, Haeusler KG, Nielsen-Kudsk JE, Berti S, Genovesi S, Marijon E, Boveda S, Tzikas A, Boriani G, Boersma LVA, Tondo C, Potter T, Lip GYH, Schnabel RB, Bauersachs R, Senzolo M, Basile C, Bianchi S, Osmancik P, Schmidt B, Landmesser U, Doehner W, Hindricks G, Kovac J, Camm AJ. An International Consensus Practical Guide on Left Atrial Appendage Closure for the Non-implanting Physician: Executive Summary. Thromb Haemost. 2024 Dec 10.

Section 6b. Factor XI inhibitors - Investigational anticoagulants

DOACs have become the standard of care for patients with NVAF [1]. However, concerns remain around the associated bleeding risk amongst vulnerable patient groups. Recently interest has focused on factor XI/XIa inhibitors in the prevention of thromboembolic complications in patients with NVAF as well as their wider use in thromboprophylaxis following major orthopaedic surgery and end stage renal disease for dialysis circuit anticoagulation [2].

Factor XI is a plasma glycoprotein that acts through the intrinsic pathway of the clotting cascade. When vascular damage occurs, factor XI is activated by thrombin (FXIa). and participates in the amplification of thrombin generation. Congenital factor XI deficiency is characterised by low risk of venous thromboembolism and ischemic stroke without an observed increased risk of spontaneous bleeding. As such factor XI/XIa is a compelling target to investigate [3].

Factor XI/XIa inhibitors can be divided into three broad molecular groups. Synthetic small molecules, such as asundexian and milvexian, bind to factor XIa and are administered orally. Monoclonal antibodies, abelacimab and osocimab, suitable for use in severe CKD, are administered intravenously or subcutaneously. Thirdly antisense oligonucleotides (ASOs) such as fesomersen, administered subcutaneously. ASOs have a slow onset of action and as such utility in NVAF may be limited [2].

The main investigational agents under investigation in NVAF are asundexian, milvexian and abelacimab.

To date two phase 2 trials have reported. It is important to highlight that these studies primarily focused on dose finding and did not compare the efficacy of the drugs for prevention of thromboembolic events.

PACIFIC AF was a dose-finding study which randomly assigned 753 individuals with AF (mean age, 74 years; nearly one-third had CKD) to receive the oral FXIa inhibitor asundexian (20 or 50 mg once daily) or apixaban (5 mg twice daily) for 12 weeks. Participants assigned to asundexian had similar or lower rates of clinical bleeding compared with those assigned to apixaban (HR 0.33, 90% CI 0.09–0.97) [3].

AZALEA-TIMI 71 investigated the role of abelacimab in 1287 participants, examining two blinded doses (150mg or 90mg) vs rivaroxaban [5]. The primary endpoint, major or clinically relevant nonmajor bleeding, for abelacimab 150 mg vs. abelacimab 90 mg vs. rivaroxaban, was: 6.1% vs. 4.9% vs. 15.4% and due to these lower rates of bleeding it was stopped early. There was also a significant reduction in major GI bleeding [4].

The phase III OCEANIC AF study was a multicentre, randomised controlled study investigating asundexian 50mg daily compared to apixaban in patients with NVAF at risk for stroke to determine the safety and efficacy of asundexian on the prevention of SSE. The trial aimed to recruit 18,000 patients although was stopped by the independent data monitoring committee due to an inferior efficacy of asundexian versus the control arm after 14830 pts had been enrolled. SSE occurred in 98 patients (1.3%) assigned to receive asundexian and in 26 (0.4%) assigned to receive apixaban (hazard

ratio, 3.79; 95% confidence interval [CI], 2.46 to 5.83) [5]. Concerns have been raised about the validity of the phase II dose finding trial as a potential explanation of the disappointing result.

There are several phase III clinical trials underway, which include:

LIBERXIA AF (NCT05757869) is a randomized, double-blind, double-dummy, parallel group, active-controlled study to evaluate the efficacy and safety of the oral factor XIa inhibitor milvexian 100mg bd, versus apixaban in participants with AF. With an estimated completion date 2027 the trial aims to recruit 15,500 patients [6].

LILAC-TIMI 76—NCT05712200 is a study to evaluate the efficacy and safety of abelacimab in high-risk patients (CHA_2DS_2VASc ≥4 OR age ≥75 and a CHA_2DS_2VASc ≥3) with AF who have been deemed unsuitable for oral anticoagulation. Recruitment is ongoing and is due to end in 2025. 1900 patients will be randomised in a 1:1 ratio to receive abelacimab 150 mg subcutaneous or matching placebo once monthly and the trial will include patients with severe renal insufficiency [6].

References

1. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, et al; Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jan 2;149(1):e1-e156.
2. Muscente F, De Caterina R. The new in anticoagulation: factor XI inhibitors, European Heart Journal Supplements.(2023);25,IssueSupplement_B:B65–B68, https://doi.org/10.1093/eurheartjsupp/suad070
3. Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet 2022; 399:1383.
4. Ruff CT, Patel SM, Giugliano RP, Morrow DA for the AZALEA–TIMI 71 Investigators. N Engl J Med 2025;392:361-371
5. Piccini JP, Patel MR, Steffel J, Ferdinand K, Van Gelder IC, et al for the OCEANIC-AF Steering Committee and Investigators. Asundexian versus Apixaban in Patients with Atrial Fibrillation. N Engl J Med 2025;392:23-32
6. Presume, J., Ferreira, J. & Ribeiras, R. Factor XI Inhibitors: A New Horizon in Anticoagulation

Section 7: Lay executive summary

People with chronic kidney disease are at an increased risk of developing a fast irregular heart rhythm known as atrial fibrillation (AF). The reasons for this aren't fully known but it may be because people with kidney disease also have other medical conditions that increase the risk. For those on dialysis shifts of fluid and components in the blood during dialysis are also thought to contribute to atrial fibrillation.

Atrial fibrillation can lead to an increased risk of developing a stroke which is caused by a blood clot travelling to the brain from the heart. But while the risk of having a stroke is known to be higher in people with kidney disease it is not known how much AF increases that risk, as the scores that are used to work it out are not tested in people with severe kidney disease.

As part of managing atrial fibrillation one discussion your clinical team may have with you is about the use of blood thinners, known as anticoagulants, to prevent blood clots forming. Anticoagulants used for patients with kidney disease include warfarin, apixaban, rivaroxaban and edoxaban. Choosing between them depends on the reason for taking an anticoagulant and how well the kidneys are functioning. People with advanced kidney disease are at a higher risk of having a bleeding episode and this risk may be further increased when taking an anticoagulant. This can lead to difficult discussions and in appendix 1 of this document is a prompt list of questions to ask that might help during these conversations with your clinical team.

If it is decided that you would benefit from an anticoagulant then the main treatment has been warfarin. However, in people with advanced kidney disease there can be difficulties with monitoring warfarin and rarely it can cause a serious condition called calciphylaxis where the small blood vessels become blocked due to calcium deposits. There are other tablet anticoagulants but the drug trials did not test their safety and how well they work in people with advanced CKD. These tablets all have some removal from the body by the kidney, however one tablet called apixaban has the least removal by the kidney and due to it being used in America and some European countries there is some data to suggest it may be similar to warfarin or even have less bleeding. In this guideline we recommend warfarin and apixaban as options for reducing the risk of having a stroke with AF for all levels of kidney function including dialysis.

There are some newer anticoagulants in development which are believed to have a lower bleeding risk but they are not yet available as they are still being tested in trials.

We have developed this guideline using the available evidence and with experts in kidney disease and anticoagulants, who have given their opinion on what we should recommend and what we need to study further. People with kidney disease who are taking anticoagulants have also been involved in developing the prompt list of questions in appendix one, and some of these patients have also taken part in developing and reviewing the guideline.

Appendix 1: Co-produced shared-decision Question Prompt list for clinicians and patients.

Parker, K., Needham, A., Thachil, J. et al. Facilitating active participation in anticoagulant decisions in advanced kidney disease: co-production of a question prompt list. BMC Nephrol 26, 42 (2025).

Anticoagulants for patients with kidney disease

Part 1- General Information

What are anticoagulants ("blood thinners")?

Anticoagulants work by affecting factors that your blood needs to clot, this means that your blood will take longer to form a blood clot.

Anticoagulants that are used in patients with kidney disease include warfarin, apixaban, rivaroxaban and edoxaban. The choice of anticoagulant depends on the reason you are taking an anticoagulant and how well your kidneys are functioning.

Why might people with kidney disease need anticoagulants?

People with kidney disease and a kidney transplant have an increased risk of developing blood clots. This may be related to specific kidney conditions but also other factors that can't be fully explained.

People with kidney disease also have an increased chance of developing a fast irregular heart rate known as atrial fibrillation. This can occur in up to a quarter of patients on haemodialysis. Atrial fibrillation can lead to blood pooling in the heart and forming a clot, this clot can then break off and lead to a stroke.

Anticoagulants are most commonly used in the treatment of blood clots and to prevent stroke in patient with atrial fibrillation, but they can also be used in blood clot prevention.

Anticoagulants are different to antiplatelets such as aspirin or clopidogrel. Antiplatelets prevent blood cells known as platelets from clumping together and forming a clot, they are mainly taken by people who have had a heart attacks or stroke.

Your clinical team will explain the reason you are taking an anticoagulant and how long you will need to take it.

What are the most common side effect of anticoagulants?

The most common side effect of anticoagulants is that it takes you longer to stop bleeding, for example if you experience a cut then you may bleed for longer. Kidney disease may also contribute to increased bleeding.

If you experience a head injury you should seek urgent medical attention to make sure there is no bleeding in your brain.

Other types of serious bleeding you may experience which requires medical attention includes:

- Heavy bleeding during a period
- Bleeding in your stool or urine
- Coughing up blood
- Blood in your sick

Part 2- Your personal anticoagulant regime

This section allows you to fill in details and write notes relating to your own personal anticoagulant regime.

My anticoagulant regime

Drug:

Dose:

Reason for taking:

Duration:

Below are some examples of questions that you may wish to discuss with your clinical team when you are being started on anticoagulants. You can use this sheet to fill in the answers to the questions you ask during the discussion.

Date of conversation _____

Name of clinician _____

Why am I taking an anticoagulant?

_____

_____

How long will I need to take my anticoagulant for?

_____

_____

What kinds of anticoagulants can be prescribed for me?

_____

What monitoring do I need to have, for example any specific blood tests?

Can I choose where this monitoring will be carried out?

What are the main side effects associated with my anticoagulant? When do I need to seek medical attention?

Does my diet or other medicines affect my anticoagulant?

What happens if I need a tooth removing or surgery?

Who will be responsible for following up on my treatment?

Who can I contact if I need help or advice? How do I contact them?

Useful resources

For further information about **warfarin:**

https://www.medicines.org.uk/emc/rmm/1081/Document

https://patient.info/medicine/warfarin-an-anticoagulant

https://www.nhs.uk/medicines/warfarin/

For further information about the direct oral acting-anticoagulants (apixaban, edoxaban, rivaroxaban):

Apixaban

https://patient.info/medicine/apixaban-tablets-eliquis

https://www.nhs.uk/medicines/apixaban/

Edoxaban

https://patient.info/medicine/edoxaban-tablets-lixiana

https://www.nhs.uk/medicines/edoxaban/

Rivaroxaban

https://patient.info/medicine/rivaroxaban-tablets-xarelto

https://www.nhs.uk/medicines/rivaroxaban/

Appendix 2: PICO for literature search and search strategies

Search strategy for section 2 run on Medline and Embase

Search terms

1 Search: (Kidney Failure, Chronic[Title/Abstract]) OR (Kidney Failure, Chronic[MeSH Terms])

2 Search: (Renal Insufficiency, Chronic[Title/Abstract]) OR (Renal Insufficiency, Chronic[MeSH Terms])

3 Search: (Renal dialysis[Title/Abstract]) OR (Renal Dialysis[MeSH Terms])

4 Search: (Kidney transplantation[Title/Abstract]) OR (Kidney Transplantation[MeSH Terms])

5 Search: (warfarin[Title/Abstract]) OR (Warfarin[MeSH Terms])

6 Search: (acenocoumarol[Title/Abstract]) OR (Acenocoumarol[MeSH Terms])

7 Search: (anticoagulan*[Title/Abstract]) OR (Anticoagulan*[MeSH Terms])

8 Search: (apixaban[Title/Abstract]) OR (apixaban[MeSH Terms])

9 Search: edoxaban[Title/Abstract]

10 Search: (rivaroxaban[Title/Abstract]) OR (rivaroxaban[MeSH Terms])

11 Search: (dabigatran[Title/Abstract]) OR (dabigatran[MeSH Terms])

12 Search: (low molecular weight heparin[Title/Abstract]) OR (low molecular weight heparin[MeSH Terms])

13 Search: (enoxaparin[Title/Abstract]) OR (enoxaparin[MeSH Terms])

14 Search: dalteparin[Title/Abstract]

15 Search: (fondaparinux[Title/Abstract]) OR (fondaparinux[MeSH Terms])

16 Search: (tinzaparin[Title/Abstract]) OR (tinzaparin[MeSH Terms])

17 Search: Ardeparin[Title/Abstract]

18 Search: bemiparin[Title/Abstract]

19 Search: certoparin[Title/Abstract]

20 Search: (nadroparin[Title/Abstract]) OR (nadroparin[MeSH Terms])

21 Search: parnaparin[Title/Abstract]

22 Search: reviparin[Title/Abstract]

23 Search: fluindione[Title/Abstract]

24 Search: (coumarin[Title/Abstract]) OR (coumarin[MeSH Terms])

25 Search: (Glomerular filtration rate[Title/Abstract]) OR (glomerular filtration rate[MeSH Terms])

26 Search: glomerular filtration rates[Title/Abstract]

27 Search: GFR[Title/Abstract]

28 Search: eGFR[Title/Abstract]

29 Search: kidney function[Title/Abstract]

30 Search: renal function

31 Search: estimat*[Title/Abstract]

32 Search: calculat*[Title/Abstract]

33 Search: (Algorithms[Title/Abstract]) OR (Algorithms[MeSH Terms])

34 Search: equat*[Title/Abstract]

35 Search: formula*[Title/Abstract]

36 Search: Modification of Diet in Renal Disease[Title/Abstract]

37 Search: MDRD[Title/Abstract]

38 Search: Chronic Kidney Disease Epidemiology[Title/Abstract]

39 Search: Chronic Kidney Disease Epidemiological[Title/Abstract]

40 Search: CKD-EPI[Title/Abstract]

41 Search: African American Study of Kidney Disease[Title/Abstract]

42 Search: AASK[Title/Abstract]

43 Search: cockcroft[Title/Abstract] AND gault[Title/Abstract]

44 Search: creatinine clearance[Title/Abstract]

45 Search: crcl[Title/Abstract]

46 Search: (Cystatin C[Title/Abstract]) OR (Cystatin C[MeSH Terms])

Search: #1 or #2 or #3 or #4 □ search 47

Search: #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 □ search 48

Search: #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 search 49

Search: #47 AND #48 AND #49 – final search

The protocol for this review has been published on the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, registration number CRD42020219449)

The following databases were used to undertake the search: Ovid MEDLINE (1946 to Feb 08 2024), Embase (1974 to 2024 Feb 08), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to Feb 08, 2024). Review papers were screened to identify any other relevant studies that had not been identified in the search. The search strategy was supported by a specialist librarian at the University of Manchester and was developed using MeSH terms and keywords relating to current anticoagulants in use.

Search Strategy for Section 3 and Section 4:

1 Kidney Failure, Chronic.mp. or Kidney Failure, Chronic

2 Renal Insufficiency, Chronic.mp. or Renal Insufficiency, Chronic

3 Renal dialysis.mp. or Renal Dialysis

4 Kidney transplantation.mp. or Kidney Transplantation

5 Heparin, Low-Molecular-Weight.mp. or Heparin, Low-Molecular-Weight

6 Heparin.mp. or Heparin

7 warfarin.mp. or Warfarin

8 acenocoumarol.mp. or Acenocoumarol

9 anticoagulants.mp. or Anticoagulants

10 apixaban.mp.

11 edoxaban.mp.

12 rivaroxaban.mp. or Rivaroxaban

13 dabigatran.mp. or Dabigatran

14 fondaparinux.mp. or Fondaparinux

15 argatroban.mp.

16 1 or 2 or 3 or 4

17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

18 16 and 17

Search strategy for Section 5

Ovid Medline (searched from inception to 13/4/24)

1. Kidney Failure, Chronic.mp. or Kidney Failure, Chronic/
2. Renal Insufficiency, Chronic.mp. or Renal Insufficiency, Chronic/
3. Renal dialysis.mp. or Renal Dialysis/
4. Kidney transplantation.mp. or Kidney Transplantation/
5. warfarin.mp. or Warfarin/
6. acenocoumarol.mp. or Acenocoumarol/
7. fluindione.mp.
8. coumarin.mp. or Coumarins/
9. anticoagulant*.mp. or Anticoagulants/
10. apixaban.mp.
11. edoxaban.mp.
12. rivaroxaban.mp. or Rivaroxaban/
13. dabigatran.mp. or Dabigatran/
14. International Normalized Ratio/ or international normalised ratio.mp.
15. international normalized ratio.mp.
16. Drug Monitoring/ or drug monitoring.mp.
17. anti factor Xa assay.mp.
18. factor Xa assay.mp.
19. factor xa.mp. or Factor Xa/
20. monitor*.mp.
21. pharmacokinetics.mp. or Pharmacokinetics/
22. pharmacodynamics.mp.
23. exp Blood Coagulation Tests/

24. ecarin clotting time.mp.

25. Biological Assay/ or assay.mp.

26. therapeutic drug monitoring.mp.

27. TDM.mp.

28. blood monitoring.mp.

29. plasma level*.mp.

30. blood level*.mp.

31. 1 or 2 or 3 or 4

32. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

33. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

34. 31 and 32 and 33

35. limit 34 to english language

Ovid Embase (searched from inception to 13/4/24)

1. Kidney Failure, Chronic.mp. or chronic kidney failure/

2. Renal Insufficiency, Chronic.mp.

3. Renal dialysis.mp. or hemodialysis/

4. home dialysis/ or dialysis/ or extended daily dialysis/ or continuous ambulatory peritoneal dialysis/ or dialysis.mp. or peritoneal dialysis/

5. Kidney transplantation.mp. or kidney transplantation/

6. *warfarin/ or warfarin.ti,ab.

7. acenocoumarol.ti,ab. or *acenocoumarol/

8. fluindione.ti,ab. or *fluindione/

9. *coumarin anticoagulant/ or coumarin.ti,ab.

10. *anticoagulant agent/

11. anticoagulant*.ti,ab.

12. apixaban.ti,ab. or *apixaban/

13. edoxaban.ti,ab. or *edoxaban/

14. rivaroxaban.ti,ab. or *rivaroxaban/
15. dabigatran.ti,ab. or *dabigatran etexilate/ or *dabigatran/
16. drug monitoring.ti,ab. or drug monitoring/
17. international normalised ratio.ti,ab. or international normalized ratio/
18. international normalized ratio.ti,ab.
19. blood clotting factor 10a/ or anti factor Xa.ti,ab.
20. factor Xa assay.ti,ab.
21. anti factor Xa assay.ti,ab.
22. pharmacokinetics/
23. pharmacokinetic*.ti,ab. or pharmacokinetic assay/ or pharmacokinetic parameters/
24. pharmacodynamic*.ti,ab. or pharmacodynamics/
25. blood coagulation test.ti,ab. or blood clotting test/
26. ecarin clotting time.ti,ab.
27. assay.ti,ab. or quantitative assay/ or pharmacokinetic assay/ or assay/
28. therapeutic drug monitoring.ti,ab.
29. TDM.mp.
30. blood monitoring.ti,ab.
31. blood level/
32. blood level*.ti,ab.
33. 1 or 2 or 3 or 4 or 5
34. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
35. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
36. 33 and 34 and 35
37. limit 36 to (english language and "remove preprint records")
38. limit 37 to (article or article in press or books or chapter or editorial or "review").

Appendix 3: Evidence tables

Supplementary Table 1. Summary of the study characteristics of included NVAF studies investigating the efficacy and safety of anticoagulation versus no anticoagulation in CKD stage 4 and non-dialysis dependent stage 5

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Chantrarat, 2020	Prospective cohort	CKD stage 3 CKD stage 4-5	CKD stage 3: Warfarin; n=978 DOAC; n=110 CKD stage 4-5: Warfarin; n=160 DOAC;n=11	CKD stage 3: No treatment; n= 270 CKD stage 4-5: No treatment; = 65	CKD stage 3: 70 CKD stage 4-5: 72.1	25.5 months	CHA_2DS_2-VASc: >2 (94.1%in CKD stage 4–5)	>3: 38% in CKD stage 4–5	Ischaemic stroke or TIA (0 and 1.2%, p = 0.554) Major bleeding (3.3% and 7.4%, p = 0.122) ICH (1.8% and 1.5%, p = 0.602) Death (10% and 6.5%, p = 0.002)
Welander, 2022	Retrospective cohort	CKD G3-G5D	Warfarin; G3: n=444 G4: n=1,011 G5: n=375 G5D: n=405	No treatment; G3: n=990 G4: n=2,830 G5: n=1,433 G5D: n=2,843	77	n/a	CHA_2DS_2-VASc: G3: 5 G4: 5 G5: 5 G5D: 5	n/a	Ischaemic stroke (HR 0.53; 95% CI 0.38–0.74) Major bleeding requiring hospitalisation (HR 1.22; 95% CI 1.02-1.46) All-cause mortality (HR 0.45; 95% CI 0.40-0.51)
Chang, 2019	Retrospective cohort	eGFR <29 ml/min/1.73m^2 including dialysis Dialysis: 25%	DOAC; n=280 (Dabigatran, Rivaroxaban, Edoxaban, Apixaban at varying doses) Warfarin; n=520	No treatment; n=2,971	DOACs: 79 Warfarin: 76 No treatment: 78	Up to 5 years or until outcome	CHA_2DS_2-VASc: DOACs: 4.7 Warfarin: 4.6 No treatment: 4.5	DOACs: 3.7 Warfarin: 4.0 No treatment: 4.0	Hospitalisation from ischaemic stroke or systemic embolism (warfarin vs. no treatment; aHR 3.1; 95% CI 2.1 – 4.6) (DOACs vs. no treatment aHR 1.1; 95% CI 0.3-3.4) Major bleeding events (warfarin vs. no treatment aHR 2.8; 95% CI 2.0-3.8) (DOACs vs. no treatment aHR 3.1; 95% CI 1.9-5.2)

Lai, 2009	Retrospective cohort	eGFR<60 ml/min/1.73m^2 eGFR<15 ml/min/1.73m^2: 33% HD: 23%	Warfarin: eGFR 30-59: 10% eGFR 15-29: 5% eGFR <15: 10% HD: 10%	No treatment: eGFR 30-59: 20% eGFR 15-29: 21% eGFR <15: 37% HD: 38%	Warfarin: 73 No treatment: 77	Warfarin: 31 months No treatment: 23 months	n/a	n/a	Thromboembolic stroke (5% vs. 21%, p < 0.05) Major bleeding (14% vs. 9%, p not significant)

Supplementary Table 2. Summary of the study characteristics of included NVAF studies investigating the efficacy and safety of VKAs versus no anticoagulation in HD patients

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s) Significant/ Not significant
Sy, 2022	Retrospective cohort Propensity matched	ESKD transitioning into dialysis	Warfarin; n=5,960	No treatment; n=22,660	77	n/a	CHA_2DS_2-VASc: Total cohort: 7 Warfarin: 7 No treatment: 7	Total cohort: 3 Warfarin: 4 No treatment: 3	Ischaemic stroke (adjusted sHR 1.44; 95% CI 1.23-1.69) Bleeding events (adjusted sHR 1.38; 95% CI 1.25-1.52)
Wakasugi, 2014	Prospective cohort Propensity matched	HD	Warfarin; n=28	No treatment; n=32	Warfarin: 67.8 No treatment: 68.4	110 person years	CHADS 2: Warfarin (n): 1: 2 2: 6 3: 4 4: 2 5: 2 6: 0 No treatment (n): 1: 2 2: 7 3: 3 4: 1 5: 3 6: 0	n/a	Ischaemic stroke (HR 3.36; 95% CI 0.67-16.66) Major bleeding (HR 0.85; 95% CI 0.19-3.64) Haemorrhagic stroke (HR 1.00; 95% CI 0.40-2.52)
Genovesi, 2015	Prospective cohort	HD	Warfarin; n=134	No treatment; n=156	> 75years: 50% in both groups	2 years or death	CHA_2DS_2-VASc: Warfarin: 0-1: 2.2% 2-4: 57.5% 5-9: 40.3% No treatment: 0-1: 5.8% 2-4: 46.1% 5-9: 48.1%	Warfarin: 0-1: 1.5% 2-3: 39.5% 4-9: 59.0% No treatment: 0-1: 0.6% 2-3: 27.6% 4-9: 71.8%	Thromboembolic events (HR 0.12; 95% CI 0.00–3.59; p = 0.2) Bleeding events (HR 3.96; 95% CI 1.15-13.68; p = 0.03)

Kai, 2017	Retrospective cohort Propensity matched	HD	Warfarin; n=888	No treatment; n=888	Warfarin: 68.9 No treatment: 67.3	2.1 years	CHA_2DS_2-VASc ≥2: Warfarin: 98.6% No treatment: 98.2%	≥3: Warfarin: 98.4% No treatment: 99.1%	All-cause death (HR 0.76; 95% CI 0.69–0.84) Ischaemic stroke (HR 0.68; 95% CI 0.52–0.91) Haemorrhagic stroke (HR 1.2; 95% CI 0.6–2.2) GI bleeding (HR 0.97; 95% CI 0.77–1.2)
Yoon, 2017	Retrospective cohort Propensity matched	HD	Warfarin; n=2,774	No treatment; n=2,774	67.6 in both groups	15.9 months	CHA_2DS_2-VASc ≥3: Warfarin: 44.7% No treatment: 44.6%	>2: Warfarin: 73.7% No treatment: 78.6%	Ischaemic stroke (HR 0.95; 95% CI 0.78–1.15; p = 0.569) Haemorrhagic stroke (HR 1.56; 95% CI 1.10–2.22; p = 0.013)
Winkelmayer, 2011	Retrospective cohort Propensity matched	HD	Warfarin; n=237	No treatment; n=948	Warfarin: 68.6 No treatment: 70.1	n/a	n/a	n/a	Ischaemic stroke (HR 0.92; 95% CI 0.61-1.37) Haemorrhagic stroke (HR 2.38; 95% CI 1.15-4.96) All-cause death (HR 1.06; 95% CI 0.90-1.24) GI bleeding (HR 0.96; 95% CI 0.70-1.31)
Akbar, 2023	Retrospective cohort	HD	Warfarin; n=44	No treatment; n=44	Warfarin: 51 No treatment: 53	11 months	CHA2DS2-VASc ≥2: 86.4%	≥3: 62.5%	All-cause death (HR 0.782; 95% CI 0.494-1.237; p = 0.293) Ischaemic stroke (HR 0.435; 95% CI 0.103-1.846; p = 0.259) Haemorrhagic stroke (HR 0.564; 95% CI 0.034-9.386; p = 0.689) MI (HR 0.337; 95% CI 0.178-0.639; p = 0.001) GI bleeding (HR 0.646; 95% CI 0.195-2.143; p = 0.476) Minor bleeding (HR 0.420; 95% CI 0.068-2.980; p = 0.351)
Genovesi, 2017	Retrospective cohort	HD	Warfarin; n=134	No treatment; n=150	76 in both groups	4 years or death	CHA_2DS_2-VASc: Warfarin: 2-4: 54% 5-9: 43.3% No treatment: 2-4: 52.8% 5-9: 42.9%	Warfarin: 2-3: 45.6% 4-9: 53.1% No treatment: 2-3: 45.6% 4-9: 53.3%	Death (HR 0.53; 95% CI 0.28–0.90; p = 0.04) Thromboembolic events (HR 0.36; 95% CI 0.13–1.05; p = 0.06) Bleeding events (HR 1.79; 95% CI 0.72–4.39; p = 0.20)
Garg, 2016	Retrospective cohort	HD	Warfarin; n=119	No treatment; n=183	Warfarin: 75 No treatment: 78	2.1 years	CHA_2DS_2-VASc: Warfarin: 2-4: 52.9% 5-9: 47.1% No treatment:	Warfarin: 2-3: 32.8% 4-9: 65.5% No treatment: 2-3: 39.9%	Ischaemic stroke (HR 0.93; 95% CI 0.49–1.82; p = 0.88) Death (HR 1.02; 95% CI 0.91–1.15; p = 0.62)

							2-4: 61.7% 5-9: 38.3%	4-9: 59.5%	Bleeding events (HR 1.53; 95% CI 0.94–2.51; p = 0.086)
Mitsuma, 2015	Retrospective cohort	HD	Warfarin; n=27	No treatment; n=55	71.2 years	3 years	n/a	n/a	All-cause death (30% vs. 49%; Log rank test p = 0.25) Ischaemic stroke/systemic embolism (11% vs. 9%; Log rank test = 0.47) Major bleeding (26% vs. 16%; Log rank test = 0.71)
Shen, 2015	Retrospective cohort	HD	Warfarin; n=1,838	No treatment; n=10,446	Warfarin: 61.8 No treatment: 61.9	1.4 years	CHADS 2 >2: Warfarin: 92.0% No treatment: 90.9%	>3: Warfarin: 70.9% No treatment: 69.3%	All-cause mortality (HR 1.01; 95% CI 0.92-1.11) Ischaemic stroke (HR 0.68; 95% CI 0.47-0.99) GI bleeding (HR 1.00; 95% CI 0.69-1.44)
Yodogawa, 2015	Retrospective cohort	HD	Warfarin; n=30	No treatment; n=54	Warfarin: 69.5 No treatment: 70.4	n/a	CHADS 2: Warfarin: 1.7 No treatment: 1.5	n/a	Stroke (HR 1.07; 95 % CI 0.20–5.74)
Chan, 2009	Retrospective cohort	HD	Warfarin; n=746	No treatment; n=925	72	1.6 years	CHADS 2: Warfarin: 2.74 No treatment: 2.58	n/a	Ischaemic stroke (HR 1.81; 95% CI 1.12-2.92) Haemorrhagic stroke (HR 2.22; 95% CI 1.01-4.91) Hospitalisation from bleeding (HR 1.04; 95% CI 0.73-1.46)

Supplementary Table 3. Summary of the study characteristics of included NVAF studies investigating the efficacy and safety of VKAs versus no anticoagulation in PD patients

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Phan, 2019	Retrospective cohort	PD	Warfarin; n=115	No treatment; n=361	Warfarin: 67.3 No treatment: 62.9	2 years	CHA_2DS_2-VASc ≥2: Warfarin: 4.6 No treatment: 4.2 p = 0.061	Warfarin: 4.6 No treatment: 4.0 p < 0.001	Death (HR 0.8; 95% CI 0.53–1.2; p = 0.28) Ischaemic stroke (HR 2.3; 95% CI 0.94–5.4; p = 0.07) Haemorrhagic stroke (HR 2.0; 95% CI 0.32–12.8; p = 0.46) GI bleeding (HR 0.92; 95% CI 0.39–2.2; p = 0.86)
Chan, 2016	Retrospective cohort	PD	Warfarin; n=67	No treatment; n=118	Mean Warfarin: 69.4 No treatment: 69.5	18 months	CHA_2DS_2-VASc: Warfarin: 3.46 No treatment: 2.97	Warfarin: 2.55 No treatment: 2.56	Ischaemic stroke (HR 0.19; 95% CI: 0.06–0.65; p = 0.01) No cases of ICH in both groups

Supplementary Table 4. Summary of the study characteristics of included NVAF studies investigating the efficacy and safety of oral anticoagulation versus no anticoagulation in CKD5d patients

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Mavrakanas, 2020	Retrospective cohort Propensity matched	HD and PD	Apixaban; n=521 5mg BD; n=207 2.5mg BD; n=257	No treatment; n=1,561	Apixaban: 68 No treatment: 69	155 days	n/a	n/a	Hospital admission for strokes, TIA, or systemic thromboembolism (HR 1.24; 95% CI 0.69-2.23) Fatal bleeding or ICH (HR 2.74; 95% CI 1.37-5.47)
Welander, 2022	Retrospective cohort	CKD G3-G5D	Warfarin; G3: n=444 G4: n=1,011 G5: n=375 G5D: n=405	No treatment; G3: n=990 G4: n=2,830 G5: n=1,433 G5D: n=2,843	77	n/a	CHA_2DS_2-VASc: G3: 5 G4: 5 G5: 5 G5D: 5	n/a	Ischaemic stroke (HR 0.49; 95% CI 0.30-0.79) Major bleeding requiring hospitalisation (HR 1.23; 95% CI 1.00-1.51)
Tan, 2017	Retrospective cohort	PD and HD	Warfarin; n=1,651	No treatment; n=4,114	74 in both groups	n/a	CHA_2DS_2-VASc (high): Warfarin: 83.5% No treatment: 84.3%	High: Warfarin: 49.0% No treatment: 50.7%	Ischaemic stroke (HR 0.88; 95% CI 0.70–1.11) Major bleeding (HR 1.50; 95% CI 1.33–1.68) GI bleeding (HR 1.03; 95% CI 0.80–1.32) Death (HR 0.72; 95%CI 0.65–0.80)
Wang, 2015	Retrospective cohort	HD and PD	Warfarin; n=59	No treatment; n=82	Warfarin: 59.8 No treatment: 62.1	4.4 years	CHA_2DS_2-VASc: Warfarin: 3.9 No treatment: 3.7	Warfarin: 3.3 No treatment: 3.5	Ischaemic stroke (HR 12.6; 95% CI 3.32-48.1; p < 0.001) ICH (HR 11.1; 95% CI 1.15-107; p = 0.038) Other bleeding events (HR 3.26; 95% CI 1.13-9.40; p = 0.028)
Shah, 2014	Retrospective cohort	HD and PD	Warfarin; n=756	No treatment; n=870	75	n/a	CHADS 2 ≥2: Warfarin: 77% No treatment: 69%	≥3: Warfarin: 84% No treatment: 86%	Stroke (aHR 1.14; 95% CI 0.78–1.67) Bleeding (aHR 1.44; 95% CI 1.13–1.85)
Olesen, 2012	Retrospective cohort	HD and PD	Warfarin; n=178	No treatment; n=678	66.8	n/a	CHA_2DS_2-VASc ≥2: 77.0%	2: 34.6% >3: 22.1%	Ischaemic stroke or peripheral artery embolism (TIA not included) (HR 0.43; 95% CI 0.25-0.74)

Supplementary Table 5. Summary of the study characteristics of included NVAF studies investigating the efficacy and safety of oral anticoagulation versus no anticoagulation in CKD5d patients (dialysis modality not specified)

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)

Kim, 2024	Retrospective cohort Propensity matched	Dialysis (modality not specified)	Oral anticoagulant (OAC); n=562	No treatment; n= 1,636	69.4	2.65 years	CHA_2DS_2-VASc: Anticoagulation: 3.9 No treatment: 3.8	n/a	All-cause death (HR 0.67; 95% CI 0.55-0.81) Ischaemic stroke (HR 0.61; 95% CI 0.41-0.89) Hospitalisation for major bleeding (HR 0.99; 95% CI 0.72-1.35)
See, 2021	Retrospective cohort Propensity matched	Dialysis (modality not specified)	Warfarin; n=448 DOACs; n=488	No treatment; n=2,977	DOACs: 74.3 Warfarin: 75.2 No treatment: 71.1	Up to 5.5 years or until study outcome	CHA_2DS_2-VASc: DOACs: 4.5 Warfarin: 4.7 No treatment: 4.1	DOACs: 3.7 Warfarin: 3.6 No treatment: 3.6	Anticoagulation vs no treatment: Ischaemic stroke or systemic embolism (HR 1.54; 95% CI 1.29-1.84; p < 0.0001) ICH (HR 1.41; 95% CI 0.99-2.02; p = 0.0550) GI bleeding (HR 1.01; 95% CI 0.83-1.22; p = 0.9384) Major bleeding (HR 1.14; 95% CI 0.97-1.34; p = 0.1222) DOACs vs. warfarin: Ischaemic stroke vs systemic embolism (HR 1.21; 95% CI 0.76-1.92; p = 0.4183) ICH (HR 0.78; 95% CI 0.29-2.10; p = 0.6255) GI bleeding (HR 1.06; 95% CI 0.65-1.74; p = 0.8187) Major bleeding (HR 0.98; 95% CI 0.64-1.51; p = 0.9373)
Agarwal, 2020	Retrospective cohort	Dialysis (modality not specified)	Warfarin; n=6,682	No treatment; n=16,089	Warfarin: 71.4 No treatment: 74.3	Up to 7.5 years or until outcome or death	CHA_2DS_2-VASc: Warfarin: 5.1 None: 6	n/a	Ischaemic CVA (HR 1.23; 95% CI 1.16-1.30) Major bleeding (HR 1.36; 95% CI 1.29-1.44) Death (HR 0.94; 95% CI 0.90-0.97)

Supplementary Table 6. Study characteristics of included NVAF studies in patients with stage 4 CKD

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Kreutz, 2024	Prospective cohort	eGFR 15-49 ml/min/1.73m^2	Rivaroxaban; n=764	VKA; n=691	78	2.1 years	CHA_2DS_2-VASc: 4 in both groups	2 in both groups	A composite of stroke or other thromboembolic events, major bleeding (HR 0.97; 95% CI 0.72-1.31) All-cause mortality (HR 0.76; 95% CI 0.59-0.98)

Chantrarat, 2020	Prospective cohort	CKD stage 3 CKD stage 4-5	Warfarin; n=1,138 DOAC; n=121	No treatment; n=335	CKD stage 3: 70 CKD stage 4-5: 72.1	25.5 months	CHA_2DS_2-VASc: >2 (94.1%in CKD stage 4–5)	>3: 38% in CKD stage 4–5	Ischaemic stroke or TIA (0 and 1.2%, p = 0.554) Major bleeding (3.3% and 7.4%, p = 0.122) ICH (1.8% and 1.5%, p = 0.602) Death (10% and 6.5%, p = 0.002)
Heleniak, 2020	Prospective cohort	eGFR 15-29 ml/min/1.73m^2	DOAC; n=90 Apixaban; n=61 Rivaroxaban; n=29	Warfarin; n=92	DOACs: 70.4 Warfarin: 68.8	26.3 months	CHA_2DS_2-VASc: DOAC: 3.1 Warfarin: 3.0	n/a	Stroke or TIA (9 [10%] vs. 7 [7.61%], p = 0.56) Major bleeding and CRNB (HR 1.12; 95% CI, 0.53-2.39)
Fu, 2023	Retrospective cohort Propensity matched	CKD stage 4 and 5 (diagnostic codes used) No dialysis patients	Warfarin; n= 6,244 Rivaroxaban; n=2,860	Apixaban; n=6,244 Apixaban; n= 2,860	78	ITT 183 days	CHA_2DS_2-VASc: 5.3-5.4	2.9 in all groups	Major bleeding (HR 1.85; 95% CI, 1.59-2.15) Ischaemic stroke (warfarin vs apixaban: HR 1.14; 95% CI 0.83-1.57) (Rivaroxaban vs apixaban: HR 0.71; 95% CI 0.40-1.24)
Ha, 2023	Retrospective cohort Propensity matched	eGFR >60 ml/min/1.73m^2 45-59 ml/min/1.73m^2 30-44 ml/min/1.73m^2 <30 ml/min/1.73m^2 No dialysis patients	Rivaroxaban; n=27,784	Warfarin; n=27,784	74	n/a	CHA_2DS_2-VASc: >2 51,508 (92.7%) matched cohort	≥3: 17,368 (31.3%)	1-year composite outcomes of all-cause death, first hospitalisation for ischaemic stroke, or TIA (pooled HR 0.78; 95% CI 0.62-0.99) First hospitalisation for major bleeding (pooled HR 0.63; 95% CI 0.37-1.09)
Lin, 2023 [3]	Retrospective cohort Propensity matched	eGFR 15-30 ml/min/1.73m^2 eGFR < 15 ml/min/1.73m^2 Chronic dialysis	VKA; n=1,335	Apixaban; n=471 Dabigatran; n=104 Edoxaban; n=130 Rivaroxaban; n=342	VKA: 71.6 DOACs: 74.2	VKAs: 2.6 years DOACs: 2.3 years	CHA_2DS_2-VASc: VKA: 4.0 DOAC: 4.2	VKA: 4.1 DOAC: 4.1	Ischaemic stroke (HR 1.05; 95% CI 0.79-1.39) Systemic thromboembolism (sHR 0.50; 95% CI 0.34-0.73) Composite of stroke and thromboembolism (sHR 0.78; 95% CI 0.62-0.98) Major bleeding (HR 0.77; 95% CI 0.66-0.90) Haemorrhagic stroke (HR 0.52; 95% CI 0.36-0.76) Composite of bleeding events (sHR 0.80; 95% CI 0.69-0.92)
Koretsune, 2022	Retrospective cohort Propensity matched	CrCl 15-49ml/min	Apixaban; n=1,394 5mg BD: 17.9% 2.5mg BD: 80.4% Other dose: 1.6%	Warfarin; n=1,394	Apixaban: 81.8 Warfarin: 81.5	Apixaban: 717 days Warfarin: 735 days	CHA_2DS_2-VASc: 3 in both groups	2 in both groups	Major bleeding events (HR 0.71; 95%CI 0.54-0.93; p = 0.01) Stroke and systemic embolism (HR 0.65; 95% CI 0.50-0.85; p < 0.01)

Fu, 2021	Retrospective cohort Propensity matched	CKD stage 1-5 eGFR <30 mL/min/1.73m^2 Warfarin; n=131 Apixaban; n=119	Warfarin; n=5,555 eGFR <30 mL/min/1.73m^2 Warfarin; n=131	Apixaban; n=1,788 eGFR <30 mL/min/1.73m^2 Apixaban; n=119	Warfarin: 68.7 Apixaban: 75.1	n/a	CHA_2DS_2-VASc: Warfarin: 3.81 Apixaban: 3.83	2.92 in both groups	Stroke and systemic embolism (aHR 0.63; 95% CI 0.40-0.98; p = 0.04) Major bleeding (standard apixaban doses: aHR 0.66; 95% CI 0.45-0.96; p = 0.03) (reduced apixaban doses: aHR 0.84; 95% CI 0.63-1.12; p = 0.23)
Weir, 2020	Retrospective cohort Propensity matched	CrCl 15-30ml/min: 81.3% CrCl<15 ml/min non-dialysis: 3.7% Dialysis: 15%	Rivaroxaban; n=781 15mg OD: 60% 20mg OD: 15% <15mg OD: 25%	Warfarin; n=781	79.9 in both groups	Up to 2 years	CHA_2DS_2-VASc: 4.5 in both groups	3.5 in both groups	Hospitalisation for ischaemic stroke or systemic embolism (HR 0.93; 95% CI 0.46-1.90; p = 0.85) Major bleeding (HR 0.91; 95% CI 0.65-1.28; p = 0.60)
Hsu, 2023	Retrospective cohort	eGFR <30 ml/min/1.73m^2 Chronic dialysis	Warfarin; n=202	DOACs; n=809 Apixaban: 25.2% Rivaroxaban: 25.4% Dabigatran: 15.3% Edoxaban: 14.1%	Warfarin: 82.5 DOACs: 83.1	Restricted to only 1 year	CHA_2DS_2-VASc: 4.5 in both groups	Warfarin: 3.6 DOACs: 3.3	Hospitalisation for stroke or systemic embolism (aHR 0.29; 95% CI 0.09-0.97) Major bleeding (aHR 0.99; 95% CI 0.34-2.92)
Kee, 2023	Retrospective cohort	Pre-dialysis CKD and ESKD	Warfarin; n=970	DOAC; n=915	Warfarin:68.4 DOACs: 73.7	23.8 months	CHA_2DS_2-VASc: VKA: 4.64 DOACs: 5.17	mHAS-BLED: Warfarin: 2.72 DOACs: 3.07	Ischaemic stroke (1.73 vs. 1.96 per 1,000 patient-years, p = 0.89) Intracranial haemorrhage (1.92 vs. 2.12 per 1,000 patient-years, p = 0.02) Gastrointestinal bleeding (1.82 vs. 1.93 per 1,000 patient-years, p = 0.02) Extracranial or unclassified major bleeding (1.84 vs. 1.99 per 1,000 patient-years, p = 0.04)
Vaitsiakhovich, 2022	Retrospective cohort	eGFR 15-60 ml/min/1.73m^2	Warfarin; n=5,903	Rivaroxaban 15mg OD; n=1,465	Warfarin: 78 Rivaroxaban: 79	Warfarin: 115 days Rivaroxaban: 119 days	CHA_2DS_2-VASc: Warfarin: 4.44 Rivaroxaban: 4.41	mHAS-BLED: 3 in both groups	Composite of ischaemic stroke and intracranial haemorrhage (HR 0.61; 95% CI 0.30–1.24) Ischaemic stroke alone (HR 0.77; 95% CI 0.33–1.82) Major bleeding (HR 1.14; 95% CI 0.83–1.58)
Welander, 2022	Retrospective cohort	CKD G3-G5D	Warfarin; G3: n=444 G4: n=1,011 G5: n=375 G5D: n=405	No treatment; G3: n=990 G4: n=2,830 G5: n=1,433 G5D: n=2,843	77	n/a	CHA_2DS_2-VASc: G3: 5 G4: 5 G5: 5 G5D: 5	n/a	Ischaemic stroke (HR 0.53; 95% CI 0.41–1.55) Major bleeding requiring hospitalisation (HR 1.22; 95% CI 1.02-1.46)
Wetmore, 2020	Retrospective cohort	eGFR<60 ml/min/1.73m^2	Apixaban; n=6,738	Warfarin; n=10,529	78	n/a	CHA_2DS_2-VASc: 5.3	3.3	Ischaemic stroke and systemic embolism Apixaban: HR 0.70; 95% CI 0.51-0.96

		No dialysis patients	Rivaroxaban; n=3,904 Dabigatran; n=1,568 (No dose information)						Rivaroxaban: HR 0.80; 95% CI 0.54-1.17 Dabigatran: HR 1.15; 95% CI 0.69-1.94 Major bleeding Apixaban: HR 0.47; 95% CI 0.37-0.59 Rivaroxaban: HR 1.05; 95% CI 0.85-1.30 Dabigatran: HR 0.95; 95% CI 0.70-1.31
Chang, 2019	Retrospective cohort	eGFR <29 ml/min/1.73m^2 including dialysis Dialysis: 25%	DOAC; n=280 (Dabigatran, Rivaroxaban, Edoxaban, Apixaban at varying doses) Warfarin; n=520	No treatment; n=2,971	DOACs: 79 Warfarin: 76 No treatment: 78	Up to 5 years or until outcome	CHA_2DS_2-VASc: DOACs: 4.7 Warfarin: 4.6 No treatment: 4.5	DOACs: 3.7 Warfarin: 4.0 No treatment: 4.0	Hospitalisation from ischaemic stroke or systemic embolism (warfarin vs. no treatment; aHR 3.1; 95% CI 2.1 – 4.6) (DOACs vs. no treatment aHR 1.1; 95% CI 0.3-3.4) Major bleeding events (warfarin vs. no treatment aHR 2.8; 95% CI 2.0-3.8) (DOACs vs. no treatment aHR 3.1; 95% CI 1.9-5.2)
Coleman, 2019	Retrospective cohort	eGFR 15-29 ml/min/1.73m^2: 15% eGFR <15 ml/min/1.73m^2: 85%	Rivaroxaban; n=1,896 20mg OD: 61.3% 15mg OD: 38.7%	Warfarin; n=4,848	72 in both groups	Until outcome or treatment discontinuation	CHA_2DS_2-VASc: 4	n/a	Stroke or systemic embolism (HR 0.55; 95% CI 0.27-1.10) Ischaemic stroke alone (HR 0.67; 95% CI 0.30-1.50) Major bleeding (32%; 95% CI 1-53%)
Di Lullo, 2018	Retrospective cohort	eGFR 15-45 ml/min/1.73m^2	Rivaroxaban 15mg OD; n=247	Warfarin; n=100	66 in both groups	16 months	n/a	n/a	Occurrence of ischaemic stroke, VTE, or TIA: 25 stroke episodes (15 haemorrhagic and 10 ischaemic) in 24 warfarin patients vs. no events in the rivaroxaban arm ($p \leq 0.002$) Occurrence of intracranial haemorrhage, GI bleeding, or other bleeding: 8 warfarin patients vs. 2 rivaroxaban patients ($p = 0.001$)
Lai, 2009	Retrospective cohort	eGFR<60 ml/min/1.73m^2 eGFR<15 ml/min/1.73m^2: 33% HD: 23%	Warfarin; n=232	No treatment; n=167	Warfarin: 73 No treatment: 77	Warfarin: 31 months No treatment: 23 months	n/a	n/a	Thromboembolic stroke (5% vs. 21%, $p < 0.05$) Major bleeding (14% vs. 9%, p not significant)

Supplementary Table 7. Study characteristics of included NVAF studies in patients with non-dialysis dependent stage 5 CKD

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Park, 2022	Prospective cohort	ESKD or dialysis	Warfarin; n= 114 DOAC; n= 48	No treatment; n= 98	Warfarin: 70 DOAC: 77	24 months	CHA_2DS_2-VASc: Warfarin: 3 DOAC: 5	Warfarin: 3 DOAC: 5 No treatment: 3	DOACs vs. Warfarin: Major or CRNM (aHR 0.11; 95% CI 0.01-0.93; p=0.043)

			Apixaban 2.5mg BD; n=22 Apixaban 1.25mg BD; n=3 Rivaroxaban 15mg OD; n=12 Rivaroxaban 10mg OD; n=2 Dabigatran 110mg BD; n=5 Edoxaban 30mg OD; n=4		No treatment: 65		No treatment: 3 p < 0.001	p = 0.028	Stroke/systemic embolism (aHR 0.33; 95% CI 0.02-6.60; p = 0.468) Myocardial infarction/critical limb ischemia (CLI) (aHR 1.17; 95% CI 0.09-15.7; p = 0.908) All-cause death (aHR 1.12; 95% CI 0.08-1.67; p=0.935) DOACs vs. no treatment: Major or CRNM (aHR 0.28; 95% CI 0.05-1.69; p=0.165) Stroke/systemic embolism (aHR 0.42; 95% CI 0.03-5.27; p = 0.501) Myocardial infarction/critical limb ischemia (CLI) (aHR 0.17; 95% CI 0.02-1.69; p = 0.130) All-cause death (aHR 0.33; 95% CI 0.06-1.98; p=0.227)
Fu, 2023	Retrospective cohort Propensity matched	CKD stage 4 and 5 (diagnostic codes used) No dialysis patients	Warfarin; n= 6,244 Rivaroxaban; n=2,860	Apixaban; n=6,244 Apixaban; n= 2,860	78	ITT 183 days	CHA_2DS_2-VASc: 5.3-5.4	2.9 in all groups	Major bleeding (HR 1.85; 95% CI, 1.59-2.15) Ischaemic stroke (warfarin vs apixaban: HR 1.14; 95% CI 0.83-1.57) (Rivaroxaban vs apixaban: HR 0.71; 95% CI 0.40-1.24)
Ha, 2023	Retrospective cohort Propensity matched	eGFR >60 ml/min/1.73m^2 45-59 ml/min/1.73m^2 30-44 ml/min/1.73m^2 <30 ml/min/1.73m^2 No dialysis patients	Rivaroxaban; n=27,784	Warfarin; n=27,784	74	n/a	CHA_2DS_2-VASc: >2 51,508 (92.7%) matched cohort	≥3: 17,368 (31.3%)	1-year composite outcomes of all-cause death, first hospitalisation for ischaemic stroke, or TIA (pooled HR 0.78; 95% CI 0.62-0.99) First hospitalisation for major bleeding (pooled HR 0.63; 95% CI 0.37-1.09)
Lin, 2023	Retrospective cohort Propensity matched	eGFR 15-30 ml/min/1.73m^2 eGFR < 15 ml/min/1.73m^2 Chronic dialysis	VKA; n=1,335	Apixaban; n=471 Dabigatran; n=104 Edoxaban; n=130 Rivaroxaban; n=342	VKA: 71.6 DOACs: 74.2	VKAs: 2.6 years DOACs: 2.3 years	CHA_2DS_2-VASc: VKA: 4.0 DOAC: 4.2	VKA: 4.1 DOAC: 4.1	Ischaemic stroke (HR 1.05; 95% CI 0.79-1.39) Systemic thromboembolism (sHR 0.50; 95% CI 0.34-0.73) Composite of stroke and thromboembolism (sHR 0.78; 95% CI 0.62-0.98) Major bleeding (HR 0.77; 95% CI 0.66-0.90) Haemorrhagic stroke (HR 0.52; 95% CI 0.36-0.76) Composite of bleeding events (sHR 0.80; 95% CI 0.69-0.92)

Xu, 2023	Retrospective cohort Propensity matched	CKD stage 4 and NDD stage 5	Apixaban 5mg BD; n=1,705 (40%)	Apixaban 2.5mg BD; n=2,608 (60%)	Apixaban 5mg BD:72 Apixaban 2.5mg BD: 80	n/a	CHA_2DS_2-VASc: 3.7 in both groups	2.5 in both groups	Stroke or systemic embolism (sHR 1.01; 95% CI 0.59–1.73) Bleeding (sHR 1.63; 95% CI 1.04-2.54) Death (sHR 1.03; 95% CI 0.77-1.38)
Sy, 2022	Retrospective cohort Propensity matched	ESKD transitioning into dialysis	Warfarin; n=5,960	No treatment; n=22,660	77	n/a	CHA_2DS_2-VASc: Total cohort: 7 Warfarin: 7 No treatment: 7	Total cohort: 3 Warfarin: 4 No treatment: 3	Stroke events (adjusted sHR 1.44; 95% CI 1.23-1.69) Bleeding events (adjusted sHR 1.38; 95% CI 1.25-1.52)
Fu, 2021	Retrospective cohort Propensity matched	CKD stage 1-5 eGFR <30 mL/min/1.73m^2 Warfarin; n=131 Apixaban; n=119	Warfarin; n=5,555 eGFR <30 mL/min/1.73m^2 Warfarin; n=131	Apixaban; n=1,788 eGFR <30 mL/min/1.73m^2 Apixaban; n=119	Warfarin: 68.7 Apixaban: 75.1	n/a	CHA_2DS_2-VASc: Warfarin: 3.81 Apixaban: 3.83	2.92 in both groups	Stroke and systemic embolism (aHR 0.63; 95% CI 0.40-0.98; p = 0.04) Major bleeding (standard apixaban doses: aHR 0.66; 95% CI 0.45-0.96; p = 0.03) (reduced apixaban doses: aHR 0.84; 95% CI 0.63-1.12; p = 0.23)
Weir, 2020	Retrospective cohort Propensity matched	CrCl 15-30ml/min: 81.3% CrCl<15 ml/min non-dialysis: 3.7% Dialysis: 15%	Rivaroxaban; n=781 15mg OD: 60% 20mg OD: 15% <15mg OD: 25%	Warfarin; n=781	80	Up to 2 years	CHA_2DS_2-VASc: 4.5	3.5 in both groups	Hospitalisation for ischaemic stroke or systemic embolism (HR 0.93; 95% CI 0.46-1.90; p = 0.85) Major bleeding (HR 0.91; 95% CI 0.65-1.28; p = 0.60)
Jun, 2017	Retrospective cohort Propensity matched	eGFR <59 ml/min/1.73m^2 excluding dialysis	Warfarin; n=7,446	No treatment; n=7,446	Warfarin: 78.2 No treatment: 78.1	1 year	CHA_2DS_2-VASc: Warfarin: 1: 22.2% 2: 36.3% 3: 23.5% 4: 9.1% 5: 2.1% 6: 0.6% No treatment: 1: 23.9% 2: 33.9% 3: 22.5% 4: 8.9% 5: 2.5% 6: 0.7%	mHAS-BLED: Warfarin: 1: 16.6% 2: 60.9% 3: 18.9% 4: 3.4% 5: 0.2% 6: 0.01% No treatment: 1: 16.6% 2: 59.1% 3: 20.0% 4: 3.9% 5: 0.4% 6: 0.01%	Stroke or TIA (HR 0.54; 95% CI 0.26-1.13; p for interaction = 0.8) Major bleeding (HR 0.95; 95% CI, 0.60-1.50; p for interaction = 0.02) Death (HR 0.62; 95% CI 0.44-0.87; p for interaction = 0.9)
Hsu, 2023	Retrospective cohort	eGFR <30 ml/min/1.73m^2 Chronic dialysis	Warfarin; n=202	DOACs; n=809 Apixaban: 25.2% Rivaroxaban: 25.4% Dabigatran: 15.3% Edoxaban: 14.1%	Warfarin: 82.5 DOACs: 83.1	Restricted to only 1 year	CHA_2DS_2-VASc: 4.5 in both groups	Warfarin: 3.6 DOACs: 3.3	Hospitalisation for stroke or systemic embolism (aHR 0.29; 95% CI 0.09-0.97) Major bleeding (aHR 0.99; 95% CI 0.34-2.92)

Kee, 2023	Retrospective cohort	Pre-dialysis CKD and ESKD	Warfarin; n=970	DOAC; n=915	Warfarin:68.4 DOACs: 73.7	23.8 months	CHA_2DS_2-VASc: Warfarin: 4.64 DOACs: 5.17	mHAS-BLED: Warfarin: 2.72 DOACs: 3.07	Ischaemic stroke (1.73 vs. 1.96 per 1,000 patient-years, p = 0.89) Intracranial haemorrhage (1.92 vs. 2.12 per 1,000 patient-years, p = 0.02) Gastrointestinal bleeding (1.82 vs. 1.93 per 1,000 patient-years, p = 0.02) Extracranial or unclassified major bleeding (1.84 vs. 1.99 per 1,000 patient-years, p = 0.04)
Welander, 2022	Retrospective cohort	CKD G3-G5D	Warfarin; G3: n=444 G4: n=1,011 G5: n=375 G5D: n=405	No treatment; G3: n=990 G4: n=2,830 G5: n=1,433 G5D: n=2,843	77	n/a	CHA_2DS_2-VASc: G3: 5 G4: 5 G5: 5 G5D: 5	n/a	Ischaemic stroke (HR 0.53; 95% CI 0.41–1.55) Major bleeding requiring hospitalisation (HR 1.22; 95% CI 1.02-1.46)
Lin, 2021	Retrospective cohort	eGFR <15ml/min/1.73m^2 including dialysis	Rivaroxaban; n=173 10mg OD; n=88 15mg OD; n=67 20mg OD; n=18	Warfarin; n=3,185	69	Up to 4 years or until outcome	CHA_2DS_2-VASc: Rivaroxaban: 0-2: 20% 3: 24% ≥4: 56% Warfarin: 0-2: 25% 3: 22% ≥4: 53%	ORBIT: Rivaroxaban: 0-2: 54% 3: 20% ≥4: 26% Warfarin: 0-2: 55% 3: 20% ≥4: 25%	Composite ischaemic stroke or systemic embolism (adjusted sHR 0.36; 95% CI 0.17-0.79; p = 0.01) Ischaemic stroke alone (adjusted sHR 0.62; 95% CI 0.24-1.61; p = 0.33) Major bleeding (adjusted sHR 0.86; 95% CI 0.50-1.47; p = 0.59) CRNB (adjusted sHR 0.74; 95% CI 0.48-1.13; p = 0.16)
Wetmore, 2020	Retrospective cohort	eGFR<60 ml/min/1.73m^2 No dialysis patients	Apixaban; n=6,738 Rivaroxaban; n=3,904 Dabigatran; n=1,568 (No dose information)	Warfarin; n=10,529	78	n/a	CHA_2DS_2-VASc: 5.3	3.3	Ischaemic stroke and systemic embolism: Apixaban (HR 0.70; 95% CI 0.51-0.96) Rivaroxaban (HR 0.80; 95% CI 0.54-1.17) Dabigatran (HR 1.15; 95% CI 0.69-1.94) Major bleeding: Apixaban (HR 0.47; 95% CI 0.37-0.59) Rivaroxaban (HR 1.05; 95% CI 0.85-1.30) Dabigatran (HR 0.95; 95% CI 0.70-1.31)
Chang, 2019	Retrospective cohort	eGFR <29 ml/min/1.73m^2 including dialysis Dialysis: 25%	DOAC; n=280 (Dabigatran, Rivaroxaban, Edoxaban, Apixaban at varying doses) Warfarin; n=520	No treatment; n=2,971	DOACs: 79 Warfarin: 76 No treatment: 78	Up to 5 years or until outcome	CHA_2DS_2-VASc: DOACs: 4.7 Warfarin: 4.6 No treatment: 4.5	DOACs: 3.7 Warfarin: 4.0 No treatment: 4.0	Hospitalisation from ischaemic stroke or systemic embolism (warfarin vs. no treatment; aHR 3.1; 95% CI 2.1 – 4.6) (DOACs vs. no treatment aHR 1.1; 95% CI 0.3-3.4) Major bleeding events (warfarin vs. no treatment aHR 2.8; 95% CI 2.0-3.8) (DOACs vs. no treatment aHR 3.1; 95% CI 1.9-5.2)
Coleman, 2019	Retrospective cohort	eGFR 15-29 ml/min/1.73m^2: 15% eGFR <15 ml/min/1.73m^2: 85%	Rivaroxaban; n=1,896 20mg OD: 61.3% 15mg OD: 38.7%	Warfarin; n=4,848	72 in both groups	Until outcome or treatment discontinuation	CHA_2DS_2-VASc: 4	n/a	Stroke or systemic embolism (HR 0.55; 95% CI 0.27-1.10)

									Ischaemic stroke alone (HR 0.67; 95% CI 0.30-1.50) Major bleeding (32%; 95% CI 1-53%)
Lai, 2009	Retrospective cohort	eGFR<60 ml/min/1.73m^2 eGFR<15 ml/min/1.73m^2: 33% HD: 23%	Warfarin; n=232	No treatment; n=167	Warfarin: 73 No treatment: 77	Warfarin: 31 months No treatment: 23 months	n/a	n/a	Thromboembolic stroke (5% vs. 21%, p < 0.05) Major bleeding (14% vs. 9%, p not significant)

Supplementary Table 8. Study characteristics of included observational studies in patients with dialysis-dependent stage 5 CKD

Reference	Study design	Renal function	Treatment (study size, n)	Control (study size, n)	Age, years (mean)	Follow-up (median)	Stroke risk (median)	Bleeding risk (HAS-BLED, median)	Study outcome(s)
Wakasugi, 2014	Prospective cohort Propensity matched	HD	Warfarin; n=28	No treatment; n=32	Warfarin: 67.8 No treatment: 68.4	110 person years	CHADS 2: Warfarin (n): 1: 2 2: 6 3: 4 4: 2 5: 2 6: 0 No treatment (n): 1: 2 2: 7 3: 3 4: 1 5: 3 6: 0	n/a	Ischaemic stroke (HR 3.36; 95% CI 0.67-16.66) Major bleeding (HR 0.85; 95% CI 0.19-3.64) Haemorrhagic stroke (HR 1.00; 95% CI 0.40-2.52)
Park, 2022	Prospective cohort	ESKD or dialysis	Warfarin; n= 114 DOAC; n= 48 Apixaban 2.5mg BD; n=22 Apixaban 1.25mg BD; n=3 Rivaroxaban 15mg OD; n=12 Rivaroxaban 10mg OD; n=2 Dabigatran 110mg BD; n=5	No treatment; n= 98	Warfarin: 70 DOAC: 77 No treatment: 65	24 months	CHA_2DS_2-VASc: Warfarin: 3 DOAC: 5 No treatment: 3 p < 0.001	Warfarin: 3 DOAC: 5 No treatment: 3 p = 0.028	DOACs vs. Warfarin: Major or CRNM (aHR 0.11; 95% CI 0.01-0.93; p=0.043) Stroke/systemic embolism (aHR 0.33; 95% CI 0.02-6.60; p = 0.468) Myocardial infarction/critical limb ischemia (CLI) (aHR 1.17; 95% CI 0.09-15.7; p = 0.908) All-cause death (aHR 1.12; 95% CI 0.08-1.67; p=0.935) DOACs vs. no treatment: Major or CRNM (aHR 0.28; 95% CI 0.05-1.69; p=0.165)

			Edoxaban 30mg OD; n=4						Stroke/systemic embolism (aHR 0.42; 95% CI 0.03-5.27; p = 0.501) Myocardial infarction/critical limb ischemia (CLI) (aHR 0.17; 95% CI 0.02-1.69; p = 0.130) All-cause death (aHR 0.33; 95% CI 0.06-1.98; p=0.227)
Konigsbrugge, 2021	Prospective cohort	HD	Phenprocoumon; n=61	No treatment; n=139	Phenprocoumon: 70 No treatment: 73	870 days	CHA_2DS_2-VASc: Phenprocoumon: 3 No treatment: 4	4	n/a
Genovesi, 2015	Prospective cohort	HD	Warfarin; n=134	No treatment; n=156	> 75years: 50% in both groups	2 years or death	CHA_2DS_2-VASc: Warfarin: 0-1: 2.2% 2-4: 57.5% 5-9: 40.3% No treatment: 0-1: 5.8% 2-4: 46.1% 5-9: 48.1%	Warfarin: 0-1: 1.5% 2-3: 39.5% 4-9: 59.0% No treatment: 0-1: 0.6% 2-3: 27.6% 4-9: 71.8%	Thromboembolic events (HR 0.12; 95% CI 0.00–3.59; p = 0.2) Bleeding events (HR 3.96; 95% CI 1.15-13.68; p = 0.03)
Lai, 2009	Retrospective cohort	eGFR<60 ml/min/1.73m^2 eGFR<15 ml/min/1.73m^2: 33% HD: 23%	Warfarin; n=232	No treatment; n=167	Warfarin: 73 No treatment: 77	Warfarin: 31 months No treatment: 23 months	n/a	n/a	Thromboembolic stroke (5% vs. 21%, p < 0.05) Major bleeding (14% vs. 9%, p not significant)
Kim, 2024	Retrospective cohort Propensity matched	Dialysis (modality not specified)	Oral anticoagulant (OAC); n=562	No treatment; n= 1,636	69.4	2.65 years	CHA_2DS_2-VASc: Anticoagulation: 3.9 No treatment: 3.8	n/a	All-cause death (HR 0.67; 95% CI 0.55-0.81) Ischaemic stroke (HR 0.61; 95% CI 0.41-0.89) Hospitalisation for major bleeding (HR 0.99; 95% CI 0.72-1.35)
Laville, 2024	Retrospective cohort Propensity matched	HD: 92% PD: 8%	DOAC; n=483 (unweighted)	VKA; n=8,471 (unweighted)	73	1.7 years	n/a	n/a	Thromboembolic events (weighted HR 0.66; 95% CI 0.46-0.94) Bleeding events (weighted HR 0.68; 95% CI 0.41-1.12)
Lin, 2023	Retrospective cohort Propensity matched	eGFR 15-30 ml/min/1.73m^2 eGFR < 15 ml/min/1.73m^2 Chronic dialysis	VKA; n=1,335	Apixaban; n=471 Dabigatran; n=104 Edoxaban; n=130 Rivaroxaban; n=342	VKA: 71.6 DOACs: 74.2	VKAs: 2.6 years DOACs: 2.3 years	CHA_2DS_2-VASc: VKA: 4.0 DOAC: 4.2	VKA: 4.1 DOAC: 4.1	Ischaemic stroke (HR 1.05; 95% CI 0.79-1.39) Systemic thromboembolism (sHR 0.50; 95% CI 0.34-0.73) Composite of stroke and thromboembolism (sHR 0.78; 95% CI 0.62-0.98) Major bleeding (HR 0.77; 95% CI 0.66-0.90) Haemorrhagic stroke (HR 0.52; 95% CI 0.36-0.76)

									Composite of bleeding events (sHR 0.80; 95% CI 0.69-0.92)
See, 2021	Retrospective cohort Propensity matched	Dialysis (modality not specified)	Warfarin; n=448 DOACs; n=488	No treatment; n=2,977	DOACs: 74.3 Warfarin: 75.2 No treatment: 71.1	Up to 5.5 years or until study outcome	CHA_2DS_2-VASc: DOACs: 4.5 Warfarin: 4.7 No treatment: 4.1	DOACs: 3.7 Warfarin: 3.6 No treatment: 3.6	DOACs vs warfarin: Ischaemic stroke or systemic embolism (HR 1.21; 95% CI 0.76-1.92; p = 0.4183) ICH (HR 0.78; 95% CI 0.29-2.10; p = 0.6255) GI bleeding (HR 1.06; 95% CI 0.65-1.74; p = 0.8187) Major bleeding (HR 0.98; 95% CI 0.64-1.51; p = 0.9373) Anticoagulation vs no treatment: Ischaemic stroke or systemic embolism (HR 1.54; 95% CI 1.29-1.84; p < 0.0001) ICH (HR 1.41; 95% CI 0.99-2.02; p = 0.0550) GI bleeding (HR 1.01; 95% CI 0.83-1.22; p = 0.9384) Major bleeding (HR 1.14; 95% CI 0.97-1.34; p = 0.1222)
Mavrakanas, 2020	Retrospective cohort Propensity matched	HD and PD	Apixaban; n=521 5mg BD; n=207 2.5mg BD; n=257	No treatment; n=1,561	Apixaban: 68 No treatment: 69	155 days	n/a	n/a	Hospital admission for stroke (ischaemic or haemorrhagic), TIA, or systemic thromboembolism (HR 1.24; 95% CI 0.69-2.23; p = 0.47) Fatal or intracranial bleeding (HR 2.74; 95% CI 1.37-5.47; p = 0.004)
Weir, 2020	Retrospective cohort Propensity matched	CrCl 15-30ml/min: 81.3% CrCl<15 ml/min non-dialysis: 3.7% Dialysis: 15%	Rivaroxaban; n=781 15mg OD: 60% 20mg OD: 15% <15mg OD: 25%	Warfarin; n=781	80	Up to 2 years	CHA_2DS_2-VASc: 4.5	3.5 in both groups	Hospitalisation for ischaemic stroke or systemic embolism (HR 0.93; 95% CI 0.46-1.90; p = 0.85) Major bleeding (HR 0.91; 95% CI 0.65-1.28; p = 0.60)
Kai, 2017	Retrospective cohort Propensity matched	HD	Warfarin; n=888	No treatment; n=888	Warfarin: 68.9 No treatment: 67.3	2.1 years	CHA_2DS_2-VASc $\geq$2: Warfarin: 98.6% No treatment: 98.2%	$\geq$3: Warfarin: 98.4% No treatment: 99.1%	All-cause death (HR 0.76; 95% CI 0.69–0.84) Ischaemic stroke (HR 0.68; 95% CI 0.52–0.91) Haemorrhagic stroke (HR 1.2; 95% CI 0.6–2.2) GI bleeding (HR 0.97; 95% CI 0.77–1.2)
Yoon, 2017	Retrospective cohort Propensity matched	HD	Warfarin; n=2,774	No treatment; n=2,774	67.6 in both groups	15.9 months	CHA_2DS_2-VASc $\geq$3: Warfarin: 44.7% No treatment: 44.6%	>2: Warfarin: 73.7% No treatment: 78.6%	Ischaemic stroke (HR 0.95; 95% CI 0.78–1.15; p = 0.569) Haemorrhagic stroke (HR 1.56; 95% CI 1.10–2.22; p = 0.013)
Winkelmayer, 2011	Retrospective cohort	HD	Warfarin; n=237	No treatment; n=948	Warfarin: 68.6 No treatment: 70.1	n/a	n/a	n/a	Ischaemic stroke (HR 0.92; 95% CI 0.61-1.37)

	Propensity matched								Haemorrhagic stroke (HR 2.38; 95% CI 1.15-4.96) All-cause death (HR 1.06; 95% CI 0.90-1.24) GI bleeding (HR 0.96; 95% CI 0.70-1.31)
Akbar, 2023	Retrospective cohort	HD	Warfarin; n=44	No treatment; n=44	Warfarin: 51 No treatment: 53	11 months	CHA2DS2-VASc ≥2: 86.4%	≥3: 62.5%	All-cause death (HR 0.782; 95% CI 0.494-1.237; p = 0.293) Ischaemic stroke (HR 0.435; 95% CI 0.103-1.846; p = 0.259) Haemorrhagic stroke (HR 0.564; 95% CI 0.034-9.386; p = 0.689) MI (HR 0.337; 95% CI 0.178-0.639; p = 0.001) GI bleeding (HR 0.646; 95% CI 0.195-2.143; p = 0.476) Minor bleeding (HR 0.420; 95% CI 0.068-2.980; p = 0.351)
Hsu, 2023	Retrospective cohort	eGFR <30 ml/min/1.73m^2 Chronic dialysis	Warfarin; n=202	DOACs; n=809 Apixaban: 25.2% Rivaroxaban: 25.4% Dabigatran: 15.3% Edoxaban: 14.1%	Warfarin: 82.5 DOACs: 83.1	Restricted to only 1 year	CHA_2DS_2-VASc: 4.5 in both groups	Warfarin: 3.6 DOACs: 3.3	Hospitalisation for stroke or systemic embolism (aHR 0.29; 95% CI 0.09-0.97) Major bleeding (aHR 0.99; 95% CI 0.34-2.92)
Wetmore, 2022	Retrospective cohort	HD	Warfarin; n=12,517	Apixaban label; n=2382 Apixaban dose below label (2.5mg BD); n=2257	Age (%) Warfarin, Apixaban label, Apixaban non-label: 18-44: 2.7, 3.7, 2.0 45-64: 34.7, 39.0, 30.0 65-74: 44.3, 43.0, 44.4 75-79: 18.3, 14.3, 23.6	567 days	CHA_2DS_2-VASc: Warfarin: 4.5 Apixaban label: 4.3 Apixaban non-label: 4.7	Warfarin: 3.0 Apixaban label: 2.9 Apixaban non-label: 3.1	Stroke or systemic embolism (HR 0.89; 95% CI 0.65-1.21) Major bleeding (HR 0.67; 95% CI 0.55-0.81) All-cause death (HR 0.85; 95% CI 0.78-0.92)
Welander, 2022	Retrospective cohort	CKD G3-G5D	Warfarin; G3: n=444 G4: n=1,011 G5: n=375 G5D: n=405	No treatment; G3: n=990 G4: n=2,830 G5: n=1,433 G5D: n=2,843	77	n/a	CHA_2DS_2-VASc: G3: 5 G4: 5 G5: 5 G5D: 5	n/a	Ischaemic stroke (HR 0.53; 95% CI 0.41–1.55) Major bleeding requiring hospitalisation (HR 1.22; 95% CI 1.02-1.46)

Lin, 2021	Retrospective cohort	eGFR<15 ml/min/1.73m^2 including dialysis	Rivaroxaban; n=173 10mg OD; n=88 15mg OD; n=67 20mg OD; n=18	Warfarin; n=3,185	69	Up to 4 years or until outcome	CHA_2DS_2-VASc: Rivaroxaban: 0-2: 20% 3: 24% ≥4: 56% Warfarin: 0-2: 25% 3: 22% ≥4: 53%	ORBIT: Rivaroxaban: 0-2: 54% 3: 20% ≥4: 26% Warfarin: 0-2: 55% 3: 20% ≥4: 25%	Composite ischaemic stroke or systemic embolism (adjusted sHR 0.36; 95% CI 0.17-0.79; p = 0.01) Ischaemic stroke alone (adjusted sHR 0.62; 95% CI 0.24-1.61; p = 0.33) Major bleeding (adjusted sHR 0.86; 95% CI 0.50-1.47; p = 0.59) CRNB (adjusted sHR 0.74; 95% CI 0.48-1.13; p = 0.16)
Agarwal, 2020	Retrospective cohort	HD	Warfarin; n=6,682	No treatment; n=16,089	Warfarin: 71.4 No treatment: 74.3	Up to 7.5 years or until outcome or death	CHA_2DS_2-VASc: Warfarin: 5.1 None: 6	n/a	Ischaemic CVA (HR 1.23; 95% CI 1.16-1.30) Major bleeding (HR 1.36; 95% CI 1.29-1.44) Death (HR 0.94; 95% CI 0.90-0.97)
Chang, 2019	Retrospective cohort	eGFR <29 ml/min/1.73m^2 including dialysis Dialysis: 25%	DOAC; n=280 (Dabigatran, Rivaroxaban, Edoxaban, Apixaban at varying doses) Warfarin; n=520	No treatment; n=2,971	DOACs: 79 Warfarin: 76 No treatment: 78	Up to 5 years or until outcome	CHA_2DS_2-VASc: DOACs: 4.7 Warfarin: 4.6 No treatment: 4.5	DOACs: 3.7 Warfarin: 4.0 No treatment: 4.0	Hospitalisation from ischaemic stroke or systemic embolism (warfarin vs. no treatment; aHR 3.1; 95% CI 2.1 – 4.6) (DOACs vs. no treatment aHR 1.1; 95% CI 0.3-3.4) Major bleeding events (warfarin vs. no treatment aHR 2.8; 95% CI 2.0-3.8) (DOACs vs. no treatment aHR 3.1; 95% CI 1.9-5.2)
Coleman, 2019	Retrospective cohort	eGFR 15-29 ml/min/1.73m^2: 15% eGFR <15 ml/min/1.73m^2: 85%	Rivaroxaban; n=1,896 20mg OD: 61.3% 15mg OD: 38.7%	Warfarin; n=4,848	72 in both groups	Until outcome or treatment discontinuation	CHA_2DS_2-VASc: 4	n/a	Stroke or systemic embolism (HR 0.55; 95% CI 0.27-1.10) Ischaemic stroke alone (HR 0.67; 95% CI 0.30-1.50) Major bleeding (32%; 95% CI 1-53%)
Phan, 2019	Retrospective cohort	PD	Warfarin; n=115	No treatment; n=361	Warfarin: 67.3 No treatment: 62.9	2 years	CHA_2DS_2-VASc ≥2: Warfarin: 4.6 No treatment: 4.2 p = 0.061	Warfarin: 4.6 No treatment: 4.0 p < 0.001	Death (HR 0.8; 95% CI 0.53–1.2; p = 0.28] Ischaemic stroke (HR 2.3; 95% CI 0.94–5.4; p = 0.07) Haemorrhagic stroke (HR 2.0; 95% CI 0.32–12.8; p = 0.46) GI bleeding (HR 0.92; 95% CI 0.39–2.2; p = 0.86)
Tan, 2019	Retrospective cohort	PD and HD	Warfarin; n=1,651	No treatment; n=4,114	74 in both groups	n/a	CHA_2DS_2-VASc (high): Warfarin: 83.5% No treatment: 84.3%	High: Warfarin: 49.0% No treatment: 50.7%	Ischaemic stroke (HR 0.88; 95% CI 0.70–1.11) Major bleeding (HR 1.50; 95% CI 1.33–1.68) GI bleeding (HR 1.03; 95% CI 0.80–1.32) Death (HR 0.72; 95%CI 0.65–0.80)

Siontis, 2018	Retrospective cohort	HD and PD	Apixaban; n=2,351 5mg BD; n=1,034 2.5mg BD; n=1,317	Warfarin; n=23,172	68 in both groups	Up to 5 years, death or anticoagulant switch	CHA_2DS_2-VASc: Apixaban: 5.27 Warfarin: 5.24	n/a	Stroke or systemic embolism (HR 0.88; 95% CI 0.69–1.12; p = 0.29) Major bleeding (HR 0.72; 95% CI 0.59–0.87; p < 0.001) Apixaban standard vs. reduced dose: Stroke or systemic embolism (HR 0.61; 95% CI 0.37–0.98; p = 0.04) Death (HR 0.64; 95% CI 0.45–0.92; p = 0.01)
Genovesi, 2017	Retrospective cohort	HD	Warfarin; n=134	No treatment; n=150	76 in both groups	4 years or death	CHA_2DS_2-VASc: Warfarin: 2-4: 54% 5-9: 43.3% No treatment: 2-4: 52.8% 5-9: 42.9%	Warfarin: 2-3: 45.6% 4-9: 53.1% No treatment: 2-3: 45.6% 4-9: 53.3%	Death (HR 0.53; 95% CI 0.28–0.90; p = 0.04) Thromboembolic events (HR 0.36; 95% CI 0.13–1.05; p = 0.06) Bleeding events (HR 1.79; 95% CI 0.72–4.39; p = 0.20)
Chan, 2016	Retrospective cohort	PD	Warfarin; n=67	No treatment; n=118	Mean Warfarin: 69.4 No treatment: 69.5	18 months	CHA_2DS_2-VASc: Warfarin: 3.46 No treatment: 2.97	Warfarin: 2.55 No treatment: 2.56	Ischaemic stroke (HR 0.19; 95% CI: 0.06–0.65; p = 0.01) No cases of ICH in both groups
Garg, 2016	Retrospective cohort	HD	Warfarin; n=119	No treatment; n=183	Warfarin: 75 No treatment: 78	2.1 years	CHA_2DS_2-VASc: Warfarin: 2-4: 52.9% 5-9: 47.1% No treatment: 2-4: 61.7% 5-9: 38.3%	Warfarin: 2-3: 32.8% 4-9: 65.5% No treatment: 2-3: 39.9% 4-9: 59.5%	Ischaemic stroke (HR 0.93; 95% CI 0.49–1.82; p = 0.88) Death (HR 1.02; 95% CI 0.91–1.15; p = 0.62) Bleeding events (HR 1.53; 95% CI 0.94–2.51; p = 0.086)
Chan, 2015	Retrospective cohort	HD	Rivaroxaban; n=244 20mg OD: 32.1% 15mg OD: 67.8% Dabigatran; n=281 150mg BD: 15.3% 75mg BD: 84.7%	Warfarin; n=8,064	Rivaroxaban: 66.9 Dabigatran: 68.4 Warfarin: 70.6	Up to 2 years	CHADS 2: Rivaroxaban: 2.2 Dabigatran: 2.3 Warfarin: 2.4	n/a	Systemic embolism: Dabigatran vs. warfarin (RR 1.71; 95% CI 0.97-2.99) Rivaroxaban vs. warfarin (RR 1.80; 95% CI 0.89-3.64) Major bleeding: Dabigatran vs. warfarin (RR 1.48; 95% CI 1.21-1.81) Rivaroxaban vs. warfarin (RR 1.38; 95% CI 1.03-1.83)
Mitsuma, 2015	Retrospective cohort	HD	Warfarin; n=27	No treatment; n=55	71.2 years	3 years	n/a	n/a	n/a
Shen, 2015	Retrospective cohort	HD	Warfarin; n=1,838	No treatment; n=10,446	Warfarin: 61.8 No treatment: 61.9	1.4 years	CHADS 2 >2: Warfarin: 92.0% No treatment: 90.9%	>3: Warfarin: 70.9% No treatment: 69.3%	All-cause mortality (HR 1.01; 95% CI 0.92-1.11) Ischaemic stroke (HR 0.68; 95% CI 0.47-0.99) GI bleeding (HR 1.00; 95% CI 0.69-1.44)
Wang, 2015	Retrospective cohort	HD and PD	Warfarin; n=59	No treatment; n=82	Warfarin: 59.8 No treatment: 62.1	4.4 years	CHA_2DS_2-VASc: Warfarin: 3.9	Warfarin: 3.3 No treatment: 3.5	Ischaemic stroke (HR 0.667; 95% CI 3.32-48.1; p = 0.482)

							No treatment: 3.7		ICH (HR 11.1; 95% CI 1.15-107; p = 0.038) Other bleeding events (HR 3.26; 95% CI 1.13-9.40; p = 0.028)
Yodogawa, 2015	Retrospective cohort	HD	Warfarin; n=30	No treatment; n=54	Warfarin: 69.5 No treatment: 70.4	n/a	CHADS 2: Warfarin: 1.7 No treatment: 1.5	n/a	Stroke (HR 1.07; 95 % CI 0.20–5.74)
Shah, 2014	Retrospective cohort	HD and PD	Warfarin; n=756	No treatment; n=870	75	n/a	CHADS 2 ≥2: Warfarin: 77% No treatment: 69%	≥3: Warfarin: 84% No treatment: 86%	Stroke (aHR 1.14; 95% CI 0.78–1.67) Bleeding (aHR 1.44; 95% CI 1.13–1.85)
Olesen, 2012	Retrospective cohort	HD and PD	Warfarin; n=178	No treatment; n=678	66.8	n/a	CHA_2DS_2-VASc ≥2: 77.0%	2: 34.6% >3: 22.1%	Ischaemic stroke or peripheral artery embolism (TIA not included) (HR 0.43; 95% CI 0.25-0.74)
Chan, 2009	Retrospective cohort	HD	Warfarin; n=746	No treatment; n=925	72	1.6 years	CHADS 2: Warfarin: 2.74 No treatment: 2.58	n/a	Ischaemic stroke (HR 1.81; 95% CI 1.12-2.92) Haemorrhagic stroke (HR 2.22; 95% CI 1.01-4.91) Hospitalisation from bleeding (HR 1.04; 95% CI 0.73-1.46)
Lai, 2009	Retrospective cohort	eGFR<60 ml/min/1.73m^2 eGFR<15 ml/min/1.73m^2: 33% HD: 23%	Warfarin; n=232	No treatment; n=167	Warfarin: 73 No treatment: 77	Warfarin: 31 months No treatment: 23 months	n/a	n/a	Thromboembolic stroke (5% vs. 21%, p < 0.05) Major bleeding (14% vs. 9%, p not significant)

Supplementary Table 9. Study characteristics of currently published RCTs in patients with dialysis-dependent stage 5 CKD

Reference (Study name)	Trial design	Dialysis modality	Intended sample size	Study drug and dose (study size)	Control group(s) (study size)	Follow-up, median (IQR)	Primary outcome(s)
Reinecke, 2023 (AXADIA-AFNET 8)	Prospective, parallel-group, multicentre	HD	222 patients for assessing superiority initially but was changed to assess non-inferiority	Apixaban 2.5mg BD; n=48	VKA; n=49	Apixaban: 429 days (37 – 1,370) VKA: 506 days (101 – 1,379)	Composite of ischaemic stroke, all-cause death, MI, and DVT or PE (p = 0.51; log rank) Composite of major bleeding, CRNM, or all-cause death (HR 0.93; 95% CI 0.53-1.65; $p_{non\text{-}inferiority}$ = 0.157)
Pokorney, 2022 (RENAL-AF)	Prospective, open-label, blinded outcome evaluation, multicentre	HD	762 patients (85% power for assessing non-inferiority)	Apixaban 5mg BD; n=55 Apixaban 2.5mg BD; n=22 Apixaban reduced to 2.5mg BD; n=5	VKA; n=72	Apixaban: 330 days (n/a) VKA: 340 days (n/a)	Time to major or CRNM bleeding (HR; 1.20; 95% CI 0.63–2.30)

De Vriese, 2021 (Valkyrie)	Prospective, open-label, parallel-group, multicentre	HD	27 patients in each arm required for 80% power	Rivaroxaban 10mg OD; n=46	VKA; n=44 Rivaroxaban 10mg OD and vitamin K2 2000µg three times a week; n=42	1.88 years (1.01 – 3.38)	Composite of fatal and non-fatal stroke, cardiac events, and other vascular events (HR 0.41; 95% CI 0.25-0.68; p = 0.0006)

Appendix 4: Authors of guideline sections

Section 1
Background, aims and concise methods
Kathrine Parker, Prof Gregory Lip, Prof Jecko Thachil

Section 2
Kidney function estimates for anticoagulant dosing
Lauren Hall, Dr Kate Bramham

Section 3
The use of risk scores for stroke and bleeding assessment
Dr John Hartemink, Dr Maria A Gauci, Prof Gregory Lip

Section 4
Treatment options for NVAF thromboprophylaxis
Isaac Tseng, Kathrine Parker, Dr Richard Buka

Section 5
Oral anticoagulant monitoring and follow up
Dr Anneka Mitchell, Dr Mark Davies, Fang Feng Ting

Section 6
Areas of interest
Dr Andrew Turley, Dr Honey Thomas

Appendix 5: List of abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AF	Atrial Fibrillation
C-G	Cockcroft-Gault
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Creatinine Clearance
DOAC	Direct Oral Anticoagulants
DOPPS	Dialysis Outcomes and Practice Patterns Study
EMA	European Medicines Agency
ESKD	End-stage kidney disease
FDA	Food and Drug Administration
HD	Haemodialysis
ICH	Intracranial haemorrhage
KDIGO	Kidney Disease Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NVAF	Non-Valvular Atrial Fibrillation
OR	Odds Ratio
PD	Peritoneal dialysis
SSE	Stroke and systemic embolism
TTR	Time in Therapeutic-Range
UGIB	Upper gastrointestinal bleed
VKA	Vitamin K antagonist