

# Oral Anticoagulant Use in Patients With Atrial Fibrillation and Chronic Kidney Disease: A Review of the Evidence With Recommendations for Australian Clinical Practice

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Chronic kidney disease is common in patients with atrial fibrillation (AF) and is associated with heightened risks of stroke/systemic embolisation and bleeding. In this review we outline the evidence for AF stroke prevention in kidney disease, identify current knowledge gaps, and give recommendations for anti-coagulation at various stages of chronic kidney disease.

Overall, anticoagulation is underused. Warfarin use becomes increasingly difficult with advancing kidney disease, with difficulty maintaining international normalised ratio (INR) in therapeutic range, increased risk of intracranial and fatal bleeding compared to non-vitamin K oral anticoagulants (NOACs), and high rates of discontinuation. Similarly, the direct thrombin inhibitor dabigatran is not recommended as it is predominantly renally excreted with consequent increased plasma levels and bleeding risk with advanced kidney disease. The Factor Xa inhibitors apixaban and rivaroxaban have less renal excretion (25–35%), modest increases in plasma levels with advancing kidney disease, and are the preferred first line choice for anticoagulation in moderate kidney disease based on strong evidence from randomised clinical trials (RCTs). In severe kidney disease there is a paucity of RCT data, but extrapolation of the pharmacokinetic and RCT data for moderate kidney disease, and observational studies, support the considered use of dose-adjusted Factor Xa inhibitors unless the bleeding risk is prohibitive. In Australia, apixaban is approved for creatinine clearance down to 25 mL/min, and rivaroxaban down to 15 mL/min. For end-stage kidney disease warfarin is the only agent approved, but we recommend against anticoagulation (except in selected cases) due to high bleeding risk, multiple co-morbidities, and questionable benefit.

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## Keywords

Non-valvular atrial fibrillation • Chronic kidney disease • Non-vitamin K oral anticoagulants • Warfarin

## Overview of Atrial Fibrillation and Anticoagulation

Atrial fibrillation (AF) is one of the most common arrhythmias faced in clinical practice, and its incidence increases linearly with worsening kidney function and albuminuria [1]. The most feared complication of AF is ischaemic stroke, caused by thromboembolism of clot from the left atrium to the brain. Many of the factors that drive stroke risk (such as congestive heart failure, hypertension, diabetes, vascular disease and increasing age) are highly prevalent in patients with chronic kidney disease (CKD). It is therefore not surprising that patients with CKD and AF are at increased risk of thromboembolic stroke and should be strongly considered for anticoagulant therapy [2].

Chronic kidney disease is defined as the presence of abnormal kidney function or structure for more than 3 months. It is classified according to the categories of estimated glomerular filtration rate (eGFR), which ranges from CKD stage 1 (normal eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>, but the presence of albuminuria, haematuria, a pathological abnormality or a structural abnormality) to CKD stage 5 (end stage kidney disease, eGFR  $< 15$  mL/min/1.73 m<sup>2</sup> and/or patient on dialysis) (Table 1) [3]. Cardiovascular morbidity and mortality increase progressively as kidney function declines. As a result, patients with CKD are 20 times more likely to die from cardiovascular events than survive to reach dialysis [4]. Some of this excess risk comes from atrial fibrillation, which is highly prevalent in CKD [5]. Patients with CKD and AF have particularly high rates of mortality and disability, particularly from ischaemic stroke and systemic thromboembolism. This risk can be significantly reduced with the use of anticoagulation, but the use of such therapies needs to be balanced against the concomitant increased bleeding risk in patients with CKD [6].

At first glance, warfarin may seem a good anticoagulant choice for patients with chronic kidney disease. Warfarin is not renally excreted, and is dose adjusted to achieve an INR of 2.0 to 3.0; this target INR applies to patients across all levels of kidney function (Table 2). In a meta-analysis of randomised controlled trials, warfarin has been shown to reduce stroke risk in AF by ~60% versus either placebo or aspirin [7]. However, the biggest drawback of warfarin is bleeding risk, with up to 30% increase in major bleeding and 30–70% increase in intracranial haemorrhage compared to non-vitamin K oral anticoagulants (NOACs) in randomised trials [8–10]. This is of particular importance in kidney disease, where there is an increased baseline risk of bleeding [2], and often both patients and physicians preferring no anticoagulation to warfarin, when that is the only available option [11]. Some of these patients are prescribed antiplatelet therapy as an alternative. However, neither aspirin

monotherapy nor dual antiplatelet therapy are adequate substitutes for warfarin or other oral anticoagulant therapy; they are significantly less effective than warfarin for stroke prevention, with similar overall bleeding risk [12,13]. Antiplatelet agents should not be used for stroke prevention in AF [14,15].

NOACs are now firmly established as the preferred therapy for stroke prevention in AF [14,15]. Three (3) NOACs are available in Australia; the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban and rivaroxaban.

The efficacy of dabigatran was established in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, involving 18,113 patients with AF at risk of stroke. Two (2) different doses of dabigatran (150 mg twice daily and 110 mg twice daily) were studied against warfarin in a 1:1:1 randomisation [8]. The 150 mg dose had better efficacy than warfarin, with similar rates of major bleeding (35% greater reduction in stroke or systemic embolism with dabigatran vs warfarin). The 110 mg dose had similar efficacy to warfarin, but significantly lower bleeding (20% lower risk of major bleeding and 70% lower risk of intracranial bleeding). Dabigatran is the only NOAC with a direct reversal agent available in the Australian market, but against this advantage is the fact it is predominantly renally excreted (80% renal elimination), resulting in two-to-three-fold higher plasma levels in patients with moderate renal impairment compared to those with normal renal function (Figure 1) [16].

Apixaban was studied in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, in which 18,201 AF patients were randomised to apixaban or warfarin [10]. The primary dose of apixaban was 5 mg twice daily, with a half dose of 2.5 mg twice daily given to patients with  $\geq 2$  of the following three criteria: age  $\geq 80$  years, weight  $\leq 60$  kg, serum creatinine

**Table 1** Stages of chronic kidney disease (Kidney Health Australia).

Stage 1	normal eGFR $\geq 90$ mL/min/1.73m <sup>2</sup> , with albuminuria, haematuria, a pathological abnormality or structural abnormality
Stage 2 (mild)	eGFR 60 to 89 mL/min/1.73m <sup>2</sup> , with albuminuria, haematuria, a pathological abnormality or structural abnormality
Stage 3a (moderate)	eGFR 45 to 59 mL/min/1.73m <sup>2</sup>
Stage 3b (moderate)	eGFR 30 to 44 mL/min/1.73m <sup>2</sup>
Stage 4 (severe)	eGFR 15 to 29 mL/min/1.73m <sup>2</sup>
Stage 5 (ESKD)	eGFR $< 15$ mL/min/1.73m <sup>2</sup> , end stage kidney disease

**Table 2** Mechanism of action and pharmacokinetics of warfarin and the NOACs.

Anticoagulant	Mechanism of Action	Half-Life	Kidney Clearance	Standard AF Dose	Reduced Dose	Recommended Dosing Relative to Food
Warfarin [41]	Vitamin K antagonist (Factors II, VII, IX and X)	40 hr	0	Blood monitoring; Dose adjustment to INR 2 to 3	-	Take with or without food (multiple foods can affect INR levels; consistent diet recommended)
Dabigatran [16]	Factor II (thrombin) inhibitor	≥50 mL/min ~14 hr >30–≤50 mL/min ~18 hr ≤30 mL/min ~28 hr	85%	150 mg BD	110 mg BD (moderate renal impairment; age ≥75 years; other factors with increased bleeding risk)	Take with or without food (with food preferred to reduce dyspepsia)
Apixaban [42]	Factor Xa inhibitor	12 hr	27%	5 mg BD	2.5 mg BD*	Take with or without food
Rivaroxaban [32]	Factor Xa inhibitor	5-9 hr (young); 11-13 hr (elderly)	35%	20 mg OD For CrCl ≥50 mL/min	15 mg OD For CrCl 15-49 mL/min	Take with food (leads to near complete absorption)

\*If ≥2 of the following features: age ≥80 years, weight ≤60 kg, serum creatinine ≥133 μmol/L.

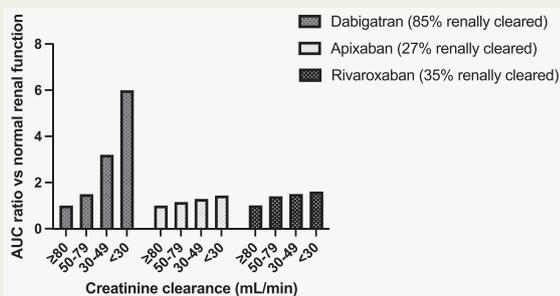
Abbreviations: INR, international normalised ratio; BD, twice daily; OD, once daily.

≥133 μmol/l. Only 428 of the 9,120 patients randomised to apixaban fulfilled these criteria and received the 2.5 mg dose. The primary endpoint (stroke or systemic embolism) was significantly lower with apixaban than warfarin (RRR 21%,  $p=0.01$  for superiority), although this was driven largely by a reduction in haemorrhagic stroke on apixaban. Rates of ischaemic stroke and systemic embolism were similar for both drugs. Other types of bleeding were also significantly lower on apixaban and overall, there was a 31% relative risk

reduction (RRR) in International Committee on Thrombosis and Haemostasis major bleeding compared to warfarin. Although only a relatively small number qualified for the 2.5 mg twice daily dose, the results in those patients who did qualify for dose reduction were consistent with the overall trial result.

The ROCKET AF trial, comparing rivaroxaban to warfarin, studied a higher risk group than either RE-LY or ARISTOTLE. To qualify for the trial, patients with AF required either a prior history of stroke or systemic embolism, or at least two of the following risk factors for stroke: ejection fraction ≤35%, hypertension, diabetes mellitus, age ≥75 years [9]. Consequently, these patients were at greater risk of stroke (and bleeding), with a mean CHADS<sub>2</sub> score of 3.5, compared to baseline CHADS<sub>2</sub> score of 2.1 in both RE-LY and ARISTOTLE. 14,264 patients were randomised to rivaroxaban or warfarin, with the rivaroxaban dose determined by renal function. The standard dose was 20 mg once daily, with dose reduction to 15 mg once daily for patients with moderate renal impairment (CKD 3, CrCl 30–49 ml per min). In this high-risk population, rivaroxaban had similar efficacy (prevention of stroke or systemic embolism) and overall bleeding rates as warfarin, but with significantly lower rates of critical bleeding, fatal bleeding, and intracranial haemorrhage [9].

Given the impressive efficacy and safety profile demonstrated in these landmark trials, NOACs are recommended



**Figure 1** Effect of kidney function on drug exposure (AUC) for dabigatran and Factor Xa inhibitors [16,32,42] Refer to PI before prescribing. No cross-study comparison intended.

Abbreviations: PI, prescriber information; AUC, area under curve.

as the preferred anticoagulant choice for stroke prevention in AF in Australian and worldwide guidelines [14,15]. The decision to anticoagulate is predominantly based on the assessment of stroke risk, with anticoagulation *considered* for patients with CHA<sub>2</sub>DS<sub>2</sub>-VA of 1 and *recommended* for a CHA<sub>2</sub>DS<sub>2</sub>-VA of 2 or more, unless the bleeding risk is felt to be too high [15]. Because many features prevalent in patients with AF (such as increased age, hypertension, and kidney disease) contribute to both stroke risk and bleeding risk, this decision is not always straightforward, but even in high-risk subgroups, the net clinical benefit is generally in favour of anticoagulation. Bleeding risk assessment scores such as the HAS-BLED<sup>1</sup> score provide opportunities to reduce bleeding risk through identification and adjustment of modifiable risk factors such as concomitant medication, hypertension, and alcohol intake. Bleeding risk scores should generally not be used as a reason to avoid treatment with oral anticoagulants [14].

## Patients With Moderate Kidney Disease (CrCl 30–49 mL/min)

Patients with moderate kidney disease are at increased risk of both stroke/systemic embolism and bleeding compared to those with normal kidney function [2]. Warfarin is of proven benefit in moderate kidney disease but has specific limitations including increased difficulty keeping patients in therapeutic range (partly driven by co-morbidities and interaction with concomitant medications), and higher risk of intracranial haemorrhage and fatal bleeding [17].

Each of the landmark trials of NOAC versus warfarin [8–10] included a substantial proportion of patients with moderate kidney disease, and therefore there is a large body of evidence to support NOAC use in this patient population. A meta-analysis of these trials showed a reduction in both stroke/systemic embolism and bleeding risk with NOACs compared to warfarin [18]. NOACs are safer and more effective than warfarin in this high-risk group and are recommended as the preferred choice in Australian and international guidelines. There are, however, important differences between individual NOACs.

Dabigatran is predominantly renally excreted and therefore drug levels and anticoagulant effect are heavily influenced by kidney function (with at least three-fold increase for CrCl 30–49 mL/min compared to normal kidney function) (Figure 1) [19]. Consequently, guidelines suggest caution with dabigatran in kidney disease and recommend the Factor Xa inhibitors (apixaban or rivaroxaban) as the preferred options [20]. Apixaban and rivaroxaban are predominantly metabolised by the liver and have relatively low renal excretion (25–35%) and only a small increase in drug levels across worsening levels of kidney function (Figure 1) [21,22].

Apixaban has been shown to have superior efficacy and safety over warfarin for patients with moderate kidney disease [23]. The ARISTOTLE trial included nearly 3,000

patients with eGFR  $\leq 50$  mL/min/1.73m<sup>2</sup>. Apixaban remained more effective than warfarin in reducing stroke or systemic embolism in these patients and caused less major bleeding [23]. In fact, the relative reduction in major bleeding was greater and the absolute benefits of apixaban more pronounced in patients with CKD, due to the higher baseline risks. This was also true of patients with rapidly deteriorating renal function (a patient group in which the variable dosing of warfarin could be a theoretical advantage). In ARISTOTLE, patients with an annual decrease in GFR of 20% or more were significantly better off on apixaban than on warfarin [24]. However, it is important to ensure patients are on the correct dose. Nearly all these patients were treated with 5 mg twice daily apixaban, and only one in 10 (149 patients) met the dose reduction criteria to receive 2.5 mg twice daily dose. Subsequent registry studies suggest there may be inadequate protection if the 2.5 mg dose is used without appropriate criteria for dose adjustment [25]. Dose reduction should only occur according to the product label; that is, when two or more of the following three criteria are present: age  $\geq 80$  years, weight  $\leq 60$  kg, serum creatinine  $\geq 133$   $\mu\text{mol/L}$ .

Rivaroxaban has the advantage of a specific dose adjustment for patients with kidney disease, with a standard 20 mg once daily dose for those with normal or mildly decreased kidney function (CrCl  $\geq 50$  mL/min), and a 15 mg once daily dose for patients with CrCl 15–49 mL/min. Pharmacokinetic data shows that this 25% reduction in dose (from 20 mg daily to 15 mg daily) adequately adjusts for the modest increase in drug levels that would otherwise be seen in kidney disease [26]. Of all the NOAC trials, ROCKET AF included the largest proportion of patients with moderate kidney disease (2,950; 21% of trial population) [27]. Nearly 1,500 AF patients with CrCl 30–50 mL/min received 15 mg rivaroxaban once daily. These patients, who by way of trial design and inclusion criteria were at high stroke risk (mean CHADS<sub>2</sub> score 3.7), had similar stroke protection on 15 mg rivaroxaban compared to dose adjusted warfarin (HR 0.84; CI 0.57–1.23) [27]. Major bleeding rates were also similar, with a trend towards more gastrointestinal bleeding offset by a reduction in fatal bleeding with rivaroxaban. In those with worsening kidney function ( $>20\%$  decrease in CrCl during study), rivaroxaban maintained at least as good an efficacy and safety profile as warfarin [28].

## Severe Kidney Disease (CrCl 15–29 mL/min)

Until recently, only warfarin was available in Australia for patients with severe kidney disease. This led to difficult treatment decisions, especially for patients with moderate kidney disease (CKD stage 3) on NOAC therapy whose kidney function declined into severe kidney disease (CKD stage 4). There is general reluctance of both patients and physicians to transition over to warfarin, and aspirin is

<sup>1</sup> Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol.

ineffective, hence patients with severe kidney disease all too often receive no anticoagulation (despite having a higher risk of stroke than patients with more modest degrees of kidney disease) [11]. Because of the exclusion criteria of the original NOAC trials, there is very little randomised data on NOAC use in severe kidney disease. However, extrapolation of trial data from patients with moderate kidney disease, pharmacokinetic data, and analyses of retrospective non-randomised datasets all support the considered use of apixaban and rivaroxaban.

Dabigatran is 80% renally excreted, and patients with CrCl <30 mL/min have six-fold higher plasma levels than those with normal kidney function (Figure 1) [29]. Dabigatran is contraindicated in patients with CrCl <30 mL/min in Australia [16].

In contrast, apixaban and rivaroxaban are predominantly metabolised by the liver and levels are only modestly affected by kidney disease. Apixaban is licenced for use down to a CrCl of 25 mL/min, based on the inclusion criteria of the ARISTOTLE trial. Only 270 patients with CrCl between 25 and 29 mL/min were enrolled, but a recently published sub-analysis of these patients shows significantly less bleeding with apixaban compared to warfarin [30].

There are no randomised controlled trials of rivaroxaban in AF patients with severe kidney disease. The ROCKET AF trial did show favourable results for rivaroxaban compared to warfarin in patients with CrCl 30–49 mL/min [27], and a non-randomised propensity matched study of AF patients with CrCl <30 mL/min (81% with CrCl 15–29 mL/min) showed that rivaroxaban had at least equivalent efficacy and safety to warfarin [31]. Accordingly, the Australian Therapeutic Goods Administration has recently approved an update to the product information for rivaroxaban allowing use in advanced kidney disease (down to a CrCl of 15 mL/min) [32]. This is a welcome development that extends treatment options for these high-risk patients.

As should always be the case when initiating anticoagulant therapy, the relative risks and benefits of treatment must be considered beforehand, and caution should be applied when there is an unmodifiable high bleeding risk or where there is concomitant medication that may increase the anticoagulation effect. Ultimately, decisions regarding initiating or continuing NOAC therapy in patients with non-valvular AF and severe kidney disease should involve specialist physician consultation, ideally including specialist nephrologist involvement with ongoing risk assessment and management.

## End-Stage Kidney Disease (CKD Stage 5, CrCl <15 mL/min)

Whether to continue (or initiate) anticoagulation for AF patients with end stage kidney disease on haemodialysis is a

more complex decision. These patients have a higher risk of bleeding, significant co-morbidities and competing risks that make the risk of stroke a less pressing issue for the majority [33]. There are no adequately powered randomised trials, and meta-analyses of observational trials of warfarin suggest a significant increase in bleeding (including haemorrhagic stroke) without a clear reduction in either ischaemic stroke or mortality in this cohort [33]. Other concerns with warfarin in this population include an increased rate of vascular calcification [34], and the potentially fatal complication of calciphylaxis. Perhaps as a consequence of these concerns, up to 70% of end-stage kidney disease (ESKD) patients initiated on warfarin discontinue it within the first year [35], and only 25% of AF patients undergoing dialysis in Australia are anticoagulated [36].

The limited data available for NOACs in CKD stage 5 suggest they cause less bleeding than warfarin, but whether they are more effective in stroke reduction and whether this outweighs the bleeding risk compared to no anticoagulation remains unclear. Only two small, randomised trials have been reported to date. The Valkyrie study, primarily designed to assess the effect of vitamin K2 on vascular calcification in ESKD, randomised 132 haemodialysis patients to warfarin, rivaroxaban 10 mg once daily, or rivaroxaban and vitamin K2 2,000 µg thrice weekly [37]. It showed significantly less bleeding, and no difference in stroke, for rivaroxaban compared to warfarin. A pharmacokinetic and pharmacodynamics study showed that a 10 mg dose of rivaroxaban in haemodialysis patients without residual kidney function resulted in drug exposure similar to a 20 mg dose in healthy volunteers [38]. The second reported randomised trial, the RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) trial, was presented at the American Heart Association annual scientific meeting in 2019 but has not yet been published in a peer reviewed journal. This trial showed no difference in bleeding, intracranial haemorrhage, stroke or cardiovascular death for patients randomised to apixaban (predominantly 5 mg twice daily) or warfarin [37]. However, the trial was ceased early due to loss of funding with only 154 patients randomised, and so was likely underpowered to detect meaningful differences in events. Both trials lacked the statistical power to assess differences in thromboembolic events, and the lack of a placebo arm means the important question of whether no anticoagulation is the safest option cannot be answered.

Non-randomised retrospective cohort analyses of NOACs in ESKD have shown conflicting results. An analysis from the US Renal Data System reported apixaban had a similar rate of stroke and systemic embolism as warfarin, but a lower risk of major bleeding [39]. However, a separate analysis from the same dataset, this time comparing apixaban with no anticoagulation, reported apixaban increased fatal and intracranial bleeding without any reduction in stroke, transient ischaemic attack or systemic embolisation [40].

**Recommendations:**

1. Anticoagulation is strongly recommended for all AF patients with moderate kidney disease (CrCl 30–49 mL/min). The preferred agents are the NOACs apixaban and rivaroxaban, levels of which are only modestly affected by kidney disease. Both medications have proven efficacy and safety against warfarin in moderate kidney disease.
2. Patients with severe kidney disease (CrCl 15–29 mL/min) should be considered for anticoagulation unless there is an unacceptably high unmodifiable bleeding risk. Apixaban (down to CrCl of 25 mL/min) and rivaroxaban (down to a CrCl of 15 mL/min) are the preferred agents.
3. Anticoagulation should not be used in patients with CKD stage 5 (including those receiving dialysis), other than in selected cases where there is likely to be substantial benefit without excess bleeding risk. In Australia, only warfarin is approved for use in CKD stage 5.

Further randomised trials are underway, including AXA-DIA (apixaban 2.5 mg twice daily vs. warfarin) (NCT02933697)<sup>2</sup>, Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis (SAFE-D) (apixaban vs. warfarin vs. no anticoagulation) (NCT03987711), and Oral Anticoagulation in Haemodialysis Patients (AVK-DIAL) (vitamin K antagonists vs. no anticoagulation) (NCT02886962), and these will give further information on whether anticoagulation with vitamin K antagonists or NOACs have a role in ESKD.

In the meantime, international guidelines emphasise the lack of evidence and recommend caution in considering anticoagulation in these patients. In Australia, NOACs are not approved for patients with CKD stage 5. Based on limited observational and trial-data in patients with atrial fibrillation and CKD stage 5, including those on dialysis, anticoagulation therapy should be individualised. The default strategy should be no anticoagulation, and clinicians and patients should make a shared decision after discussion of the benefits and harms of treatment options, taking into consideration patients' competing risks, values, and preferences.

## Conclusions

Anticoagulation is strongly recommended for all AF patients with moderate kidney disease (CrCl 30–49 mL/min) and a CHA<sub>2</sub>DS<sub>2</sub>-VA risk  $\geq 2$ , unless there is an unacceptably high bleeding risk without reversible cause. Anti-platelet therapy is ineffective for stroke prevention in AF, and NOACs are first line therapy (over warfarin). Apixaban and rivaroxaban are preferred over dabigatran (levels of which increase substantially with kidney disease). Care should be taken to choose the correct apixaban dose to avoid either excessive or inadequate anticoagulation: the full dose (5 mg twice daily) should be used in moderate kidney disease unless the patient meets at least two criteria (age  $\geq 80$  yrs, weight  $\leq 60$  kg, serum creatinine  $\geq 133$   $\mu\text{mol/L}$ ) for dose reduction to 2.5 mg twice daily. Rivaroxaban has a specific dose for patients with chronic kidney disease, with 15 mg once daily proven safe and effective for patients with moderate kidney disease.

Patients with severe kidney disease (CrCl 15–29 mL/min) are often at high risk of both stroke and bleeding. The decision to anticoagulate should take into account these competing risks. If the decision is made to anticoagulate, the limited data available suggests NOACs (apixaban or rivaroxaban) are preferable to warfarin, which is often poorly tolerated, with difficulty maintaining adequate time in therapeutic range and high rates of discontinuation. In Australia, apixaban is licenced for use down to CrCl of 25 mL/min, and rivaroxaban is licenced for use down to a CrCl of 15 mL/min.

Patients with end stage kidney disease have high bleeding risk and multiple competing co-morbidities. Unless stronger data suggesting a net clinical benefit for anticoagulation in these patients becomes available, warfarin and NOACs should not be used in patients with CKD stage 5, including those receiving dialysis, other than on a carefully considered case-by-case basis.

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