

# Efficacy and safety of new direct oral anticoagulants in chronic kidney disease: AHA 2019 updated guidelines and review of the literature



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## Abstract

Direct oral anticoagulants (DOACs) are the drug of choice for the treatment of atrial fibrillation-associated systemic embolism and reducing the risk of strokes in chronic kidney disease (CKD) patients. DOACs have fewer drug-to-drug interactions as well as fewer side effects, compared to warfarin. This article compiled up-to-date research on the use of DOACs in CKD patients, taking the AHA 2019 guidelines into consideration. The aim of this article was to compare the efficacy and safety of DOACs with warfarin and to assess whether DOACs are a better alternative to warfarin. Among DOACs, apixaban has been shown to have the best outcome compared to other DOACs. As a result, the AHA 2019 updated guidelines have recommended warfarin and apixaban to be the first line agents for CKD patients. This review concluded that DOACs are better option in patients with mild to moderate CKD and excluding apixaban other DOACs are not indicated in patients with CrCl < 25 ml/min.

**Key words:** direct oral anticoagulants, chronic kidney disease.

## Introduction

A number of pivotal phase-3 trials of direct oral anticoagulants (DOACs) have been shown to yield more desirable results in preventing embolism in the population with atrial fibrillation (AFib) and decreasing stroke incidence, in addition to reducing bleeding [1]. However, all of these studies were carried out in subjects with a glomerular filtration rate (GFR) of > 30 ml/min and patients on dialysis or those with advanced chronic kidney disease (CKD) were excluded from their studies [1]. CKD is widely defined as a GFR < 60 ml/min for a minimum of 3 months, and has varying prevalence in different regions, being highly associated with aging populations.

Chronic kidney disease and end stage renal disease (ESRD) remains a significant health problem and a rapid

## Streszczenie

Nowe doustne antykoagulanty (NOAC) są stosowane w profilaktyce udaru mózgu lub zatorowości obwodowej u pacjentów z migotaniem przedsionków i przewlekłą chorobą nerek (PChN). NOAC odznaczają się mniejszym odsetkiem interakcji oraz mniejszym odsetkiem skutków ubocznych w porównaniu z warfaryną. Artykuł stanowi podsumowanie dotychczasowych publikacji poświęconych tej tematyce, w tym wytycznych *American Heart Association* (AHA) z 2019 r. Celem artykułu jest porównanie skuteczności i bezpieczeństwa NOAC z warfaryną i ocena, czy NOAC są lepszym wyborem niż warfaryna. Wykazano, że wśród wszystkich preparatów NOAC najlepszymi parametrami cechuje się epiksaban. W związku z tym zaktualizowane wytyczne AHA z 2019 r. zalecają warfarynę i apiksaban w PChN. Ponadto NOAC stanowią lepszą opcję leczenia u pacjentów z łagodną i umiarkowaną PChN i wyłączając apiksaban, inne NOAC nie są wskazane u pacjentów z CrCl < 25 ml/min.

**Słowa kluczowe:** nowe doustne antykoagulanty, przewlekła choroba nerek.

rise has been reported from the late 1990s to 2019. The current prevalence of CKD in the United State (US) as of 2018 is 15%, which is up by almost 3% since 2015 [2]. These patients are at a higher risk of non-valvular AFib as well as an increased incidence of haemorrhage. This bleeding tendency is due to uraemia-induced platelet dysfunction and abnormalities in subendothelial interaction, with increased procoagulation and reduced endogenous anticoagulation [3]. Patients on haemodialysis have an added risk of bleeding due to the administration of heparin, repeated dialysis membrane interaction, vascular access cannulation and increased blood pressure. The introduction of four new DOAC, namely edoxaban, apixaban, rivaroxaban and dabigatran, has broadened the options of anticoagulation in patients with CKD and AFib. These agents have been shown to have

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decreased the frequency of bleeding, embolism, and risk of stroke, and have widely been prescribed for patients with CKD, ESRD and calciphylaxis [4].

The prevalence of AFib is directly proportional to the kidney function, with an increase in AFib as the GFR decreases. The incidence of AFib is as much as 15% higher in CKD patients compared to healthy age-matched control groups [5]. The most recent 2019 American Heart Association (AHA) guideline for the management of patients with AFib and CKD has been modified. Apixaban, dabigatran and rivaroxaban are approved to be used for patients with CrCl < 15 ml/min, CrCl 15–30 ml/min, and CrCl < 50 ml/min respectively. All of these medications have a IIb (Benefit ≥ Risk) Class of Recommendation (COR) with 'B-R' (Moderate quality) as Level of Evidence (LOE). While the use of DOACs such as rivaroxaban, dabigatran or edoxaban is not recommended in patients with AFib and ESRD, LOE is updated from 'Limited data' to 'Expert Opinion' with COR of III (Benefit = Risk) [6].

Despite the lack of evidence showing the efficiency of DOACs in large-scale trials and the above updated recommendations, many physicians are still prescribing these drugs to their patients [7]. This is concerning because all of these agents rely on kidneys for excretion. Chan *et al.* reported that around 12% of patients on dialysis with AFib and 24% of patients with advanced CKD were prescribed DOACs. Apixaban was the most common DOACs at 10.4% in CKD and 10.5% in dialysis patients ( $n = 102,504$  and  $n = 140,918$ ) respectively [1]. Oral anticoagulants such as warfarin are not largely prescribed, even with evidence of AFib associated thrombo-embolism in CKD patients, in fear of excessive bleeding complications [8]. Nonetheless, warfarin, a vitamin K antagonist (VKA), is still the best choice of anticoagulant in AFib patients. A large clinical study of warfarin in 2014 showed protection from cardiovascular events without any increased risk of bleeding [9]; however, Nochaiwong in 2016 reported that warfarin actually increased the frequency of bleeding and did not reduce ischaemic events, strokes or the number of deaths [10].

This review article summarises the up-to-date available pharmacology of commonly used DOACs, and their efficacy in preventing stroke as well as reducing bleeding risks. This article focuses mainly on patients suffering from AFib and CKD. In addition, the use of DOACs in advanced kidney disease and dialysis will be discussed before determining their use in these particular subjects. This article will also concisely review the AHA 2019 guidelines and the various changes that have occurred since 2014.

### Pharmacokinetics of drugs in CKD

The ability of the kidney to remove uric acid from the body decreases as the GFR declines, resulting in an increase in uraemia. Uraemia has a negative effect on pharmacokinetics (PK), by impairing plasma protein binding and as a result increasing the drug levels in the body. Renal excreted drugs are cleared through the glomerulus and rarely by tubular secretion. Therefore, reduced GFR results in an

increased half time and increased level of drug, which leads to toxicity from supra-therapeutic levels in the body [10]. Consequently, the area under the curve (AUC) increases, requiring an appropriate dose adjustment.

In clinical practice, dosing of anticoagulants is estimated using a formula and one single serum creatinine level. In contrast, the Cockcroft-Gault formula is used to calculate renal function when DOACs are used. This method has been shown to overestimate by 10–40%; therefore, novel equations such as 'Modification of Diet in Renal Disease', and 'Chronic Kidney Disease Epidemiology Collaboration' have consistently proved to be more precise [11].

### Warfarin

Warfarin is a VKA drug, which was approved to be used as an anticoagulant in the mid nineteenth century. Warfarin is minimally dependent on renal excretion as it is 99% bound to plasma proteins and its elimination is through the hepatic metabolism. The same property makes warfarin non-dialyzable and drug-to-drug interaction should be carefully managed as these patients are on a multi-drug regimen. Reversal of warfarin with low doses of vitamin K or fresh-frozen plasma, as well as wide availability and low cost, makes its use desirable in everyday life [12]. Limdi *et al.* in their study concluded that CKD patients are at an increased risk of bleeding and a dose reduction is required (10% in patients with GFR of 30–59) [13]. Despite a black box warning of the use of warfarin by the FDA in patients with CKD, as it is known to increase haemorrhage, it is still widely used [7]. In fact, the AHA 2019 updated guideline still recommends warfarin as the first-choice treatment in treating AFib patients suffering from CKD, followed by the second choice of apixaban [6]. The use of enoxaparin, among other low molecular weight heparins (LMWH), has been shown to be contraindicated in patients with CKD stage 4–5 due to the accumulation of the drug and the increased risk of major bleeding [14].

### Direct oral anticoagulants (DOACs)

Currently, to our knowledge, the FDA has approved four DOACs for the prevention of AFib associated thrombo-embolism; these are: dabigatran, apixaban, edoxaban and rivaroxaban. Thorough management of these DOACs, and dosing regulation, adverse side effects and reversal agents have become paramount in clinical practice. Studies have been carried out to tackle these issues and some of the antidotes of DOACs are shown in Table I [7, 15, 16].

Appropriate DOAC dose reductions rely on the level of renal function and currently approved doses of these regimens in CKD I-III in Europe are shown in Table II [17, 18]. DOACs in many studies have proved to be more efficient and safer than VKA when the GFR is > 60 ml/min. In addition, patients on DOACs with a CrCl 30–50 ml/min were shown to have fewer bleeding complications and had similar effectiveness compared to warfarin. However, the use of VKA surpasses DOACs in individuals with GFR less than 30 ml/min, especially dabigatran, which has the highest percent-

**Table I.** DOACs and their reversal antidotes

Reversal agent	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Specific antidote	Idarucizumab	Andexanet alfa	–	–
Fresh frozen plasma	No	Yes	Yes	Yes
Factor VIII inhibitor bypass	Yes	Yes	Yes	Yes
Haemodialysis	Yes	No	No	No

**Table II.** Properties of different DOACs and drug regimens in patients suffering from CKD

Drug	Kidney elimination (%)	Peak effect [h]	Renal function (CrCl [ml/min])			
			51–80	30–50	15–29	< 15
Dabigatran	80	1–3	220 mg twice/day	150 mg once/day	Not indicated	Not indicated
Apixaban	25	1–2	2.5 mg twice/day	2.5 mg twice/daily	Use with caution	Not recommended
Edoxaban	35	1–2	60 mg once/day	30 mg once/day	30 mg once daily	Not recommended
Rivaroxaban	33	2–4	10 mg once/day	10 mg once/day	Use with caution	Not indicated

age renal elimination [19]. Numerous studies have shown that DOACs significantly reduce the risk of embolism, strokes and intracranial bleeding events while increasing GI bleeding compared to VKA use (Table III) [20–23]. However, a study published by Jun et al. did not show any association of GI bleeding with the use of DOACs [24].

### Direct thrombin inhibitor drugs

#### Dabigatran

Dabigatran is a direct thrombin inhibitor and dabigatran etexilate at 150 mg twice daily is the first DOAC to be approved by the FDA for prevention of embolisms and strokes for population with CrCl > 30 ml/min. This drug is coated with a tartaric acid core, which augments bioavailability at a lower pH and this core is associated with causing dyspepsia and GI bleeding [25]. Prothrombin time (PT) has been shown to be better than APTT in measuring the concentration of dabigatran, but it does not differentiate between sub-therapeutic and therapeutic doses [26]. Therefore, the ecarin-clotting time (derived when ecarin cleaves prothrombin to meizothrombin) has been shown to be highly sensitive and strongly correlates with dabigatran concentration. A parallel-group study on the PK and PD of dabigatran in 23 patients with CKD showed a higher area under the plasma concentration-time curve values in subjects with CrCl 50–80 ml/min (1.5 times higher), 30–50 ml/min (3.2 times higher) and < 30 ml/min (6.3 times higher) compared to healthy individuals. In addition, the time of drug elimination increased two fold from 14 hours to 28 hours in patients with severe kidney disease [27].

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, 6,015 patients were given low-dose (110 mg) dabigatran, 6,076 subjects were treated with a higher dose (150 mg) twice daily and 6,022 were given warfarin. After 2 years of follow-up, they observed a lower incidence of strokes, MI, PE, hospitalisation, vascular deaths and major haemorrhages in subjects treated

**Table III.** Large-scale clinical studies of DOACs and their outcome in terms of stroke and GI bleeding compared to warfarin use

Study	Sample size	HR (95% CI) of stroke	HR (95% CI) of GI bleeding
Lauffenburger [20]	6727	0.76	1.52
Graham [21]	134,414	0.80	1.28
Romanelli [22]	348750	0.92	1.23
Patel [23]	7111	0.85	3.15

with dabigatran compared to warfarin. The results of the study are summarised in Table IV [28, 29].

Warfarin was the only drug of choice in preventing embolisms in AFib patients preceding the RE-LY study. However, the RE-LY study demonstrated the 150-mg dabigatran regimen to be significantly superior in terms of low bleeding and stroke rates in comparison to warfarin. Additional studies have shown that the risk of systemic embolism increases as the CrCl decreases in subjects given dabigatran [30]. In the RE-LY study, patients with severe kidney disease were excluded; therefore the FDA carried out a study on 3,343 subjects with a GFR of 30–50 ml/min. They concluded that the high dosage of dabigatran had a greater benefit with regards to reducing strokes and systemic embolisms, as well as low bleeding in comparison to 110 mg dosage [31]. Subsequently, the FDA approved a 150 mg dose of dabigatran to be used in patients with CrCl 30–50 ml/min, and 75 mg twice daily in CrCl 15–30 ml/min, to lower the likelihood of embolisms and strokes [31]. A model simulation confirmed that 75 mg daily dabigatran lowered the steady-state peak by 31% and trough levels by 42% compared to the higher dose (150 mg) twice a day in CKD patients [31].

One session of haemodialysis (4 hours) has been shown to remove as much as 60% of dabigatran, making it the only DOAC to be removed by this method. Therefore, patients undergoing haemodialysis are not recommended dabigatran for anticoagulation [27].

**Table IV.** Treatment regimens and their outcome in the RE-LY study

Outcome	Warfarin versus low dose dabigatran	Warfarin versus high dose dabigatran
Systemic emboli or stroke (%)	1.69 vs. 1.53	1.69 vs. 1.11
Relative risk (95 % CI)	0.91 (0.74–1.11)	0.66 (0.53–0.82)
P-value	< 0.001	< 0.001
Stroke (%)	1.6 vs. 1.4 ( $p = 0.41$ )	1.6 vs. 1.0 ( $p < 0.001$ )
Cardiac ischaemia (%)	0.53 vs. 0.72	0.53 vs. 0.74
Pulmonary embolism (%)	0.09 vs. 0.12 ( $p = 0.56$ )	0.09 vs. 0.09 ( $p = 0.21$ )
Hospitalization (%)	20.8 vs. 19.4 ( $p = 0.003$ )	20.8 vs. 20.2 ( $p = 0.34$ )
Death related to vessels (%)	2.69 vs. 2.43 ( $p = 0.21$ )	2.28 vs. 2.69 ( $p = 0.04$ )
Major haemorrhage (%)	3.36 vs. 2.71 ( $p = 0.003$ )	3.36 vs. 3.11 ( $p = 0.31$ )
Mortality (%)	4.13 vs. 3.75 ( $p = 0.13$ )	4.13 vs. 3.64 ( $p = 0.051$ )

**Table V.** Comparison of clinical outcome of patients treated with apixaban and warfarin

Parameter	Apixaban	Warfarin	HR	95% CI	P-value
Major bleeding (% per-year)	2.13	3.09	0.69	0.60–0.80	< 0.001
All-cause mortality (% per-year)	3.52	3.94	0.89	0.80–0.99	< 0.047
Haemorrhagic stroke (% per-year)	0.24	0.47	0.51	0.35–0.75	0.001
Ischaemic stroke (% per-year)	0.97	1.05	0.92	0.74–1.13	0.42

### Factor Xa inhibitors

#### Apixaban

In the ARISTOTLE trial, apixaban was compared with warfarin in over 18,000 patients suffering from AFib with one extra risk factor of stroke. The results of the study are summarised in Table V. They established apixaban to be significantly better compared to warfarin in terms of lowering mortality, lowering bleeding and preventing strokes or systemic emboli formation [32]. Consequently, the FDA approved the use of apixaban (2.5 mg) twice a day for patients who are either less than 60 kg, or aged greater than 80 years old and with creatinine of  $\leq 1.5$  mg/dl. However, in 2014 the dosage for patients suffering from ESRD or those undergoing dialysis was amended. For these patients 5 mg twice daily was suggested, unless they were either  $\leq 60$  kg or age  $\geq 80$  years old, in which case 2.5 mg twice per day is still used [1]. A double-blinded control trial found that apixaban had 55% lower incidence of embolism compared to aspirin for patients who tried and failed warfarin treatment [33].

The ARISTOTLE randomised controlled clinical trial, however, excluded subjects with advanced CKD and ESRD. Wang *et al.*, in a parallel group single-dose study, compared 8 haemodialysis patients with 8 healthy patients. They found that patients with ESRD off haemodialysis had a 10% decrease

in Cmax and 36% increase in AUC compared to healthy individuals who were given 5 mg apixaban. Also ESRD patients undergoing haemodialysis had a reduction in apixaban AUC and Cmax of 14% and 13% respectively [34].

Another open-labelled study of apixaban tolerance and safety at 10 mg single dose showed that AUC increased to almost 45% in subjects with GFR  $< 15$  in comparison to healthy patients with normal renal function [35]. Therefore, these studies suggest that current dosing for apixaban could increase drug levels by up to 45% in ESRD patients. Despite all these studies the use of apixaban is recommended in the 2019 AHA guidelines in patients with advanced CKD [6].

#### Edoxaban

Edoxaban is the most recent FDA approved DOAC after a trial that confirmed edoxaban non-inferiority compared to VKA in patients with AFib. ENGAGE AF-TIMI 48, a randomised controlled study of over 21,000 patients, compared two different dose regimens of edoxaban and warfarin in terms of preventing systemic embolism and strokes. As with the RE-LY study, patients with CrCl  $< 30$  ml/min were also excluded; however, those with a CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> score of  $> 2$  were included in the ENGAGE AF-TIMI trial [36]. The results of the study are summarised in Table VI.

**Table VI.** Comparison of warfarin with 30 mg and 60 mg of edoxaban

Outcome (bleeding)	Warfarin vs. 30 mg edoxaban		Warfarin vs. 60 mg edoxaban	
	% People per year	HR (95%CI)	% People per year	HR (95%CI)
Stroke	0.85 vs. 0.26	0.30 (0.21–0.43)	0.85 vs. 0.39	0.47 (0.34–0.63)
GI bleeding	1.23 vs. 0.82	0.67 (0.53–0.83)	1.23 vs. 1.51	1.23 (1.02–1.50)
Life-threatening bleeding	0.78 vs. 0.25	0.32 (0.23–0.46)	0.78 vs. 0.40	0.51 (0.38–0.70)
Fatal	0.38 vs. 0.13	0.35 (0.21–0.57)	0.38 vs. 0.21	0.55 (0.36–0.84)

**Table VII.** Comparison of four DOACs and their associated incidence of stroke and bleeding

CrCl < 50 ml/min	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Hazard ratio of stroke	0.56	0.79	0.87	0.88
Hazard ratio of major bleeding	1.01	0.50	0.76	0.98

In summary, both 30 mg and 60 mg of edoxaban were non-inferior to VKA in terms of efficacy and prevention of strokes. This study was followed by a post hoc analysis on 1,202 subjects with GFR < 30 ml/min, which illustrated lower frequency of strokes as well as less major bleeding in subjects treated with edoxaban compared to warfarin [1]. A further study by Korestsune *et al.* compared 50 patients (CrCl 15–30 ml/min) taking 15 mg of edoxaban to 22 and 21 patients with normal renal receiving 30 or 60 mg of edoxaban respectively. The rate of bleeding was comparable in all three treatments: 20.7% bleeding (30 mg) and 23.8% bleeding in patients receiving 60 mg of edoxaban. They concluded that administering 15 mg to patients with severe CKD has similar safety and efficacy compared to normal or mild renal impairment [37].

Surprisingly, subjects with CrCl > 95 ml/min proved to have a higher risk of stroke when treated with edoxaban compared to warfarin (HR = 2.16, 95% CI: 1.17–3.07) due to a decrease in plasma drug concentration [38]. The kidneys clear around 50% of edoxaban and a single session of dialysis cleans only 9% of the total drug.

### Rivaroxaban

Rivaroxaban is a factor Xa inhibitor, also used for the prevention of strokes and systemic embolisms in patients with AFib. The ROCKET AF randomised trial of > 14,000 patients suffering from AFib and having a CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> ≥ 2 with CrCl > 30 ml/min demonstrated 20 mg rivaroxaban once a day to be non-inferior to VKA at reducing strokes and embolisms [25]. The dosage decreased to 15 mg daily for subjects with CrCl 30–50 ml/min. Nonetheless, there was no difference in the outcome with reduced dosage or 20 mg compared to warfarin [39]. In addition, preventing stroke in patients with CrCl 30–50 ml/min and those with > 50 was very similar: HR = 0.85, 95% CI: 0.16–1.08 for CrCl 50–80 ml/min and HR = 0.88, 95% CI: 0.65–1.19 for patients with CrCl 30–50 ml/min [39]. These results were further reinforced by DeVriese *et al.*, who established that patients with ESRD given 10 mg and healthy patients given 20 mg had similar AUCs [40]. Conversely, other studies oppose this and reported an increase of over 5% in AUC in patients with ESRD treated with a 15 mg dose.

A further PK/PD study demonstrated that rivaroxaban is accumulated in patients with ESRD and an increased systemic exposure therefore requires a dose reduction. The FDA and AHA/ACC/HRS have not recommended rivaroxaban in patients undergoing dialysis, and it has been shown to be poorly cleared by haemodialysis [6].

The hazard ratio (HR) of strokes and other major bleeding using four DOACs compared to warfarin is shown in

Table VII. It is clear that all DOACs are significantly more effective in reducing strokes and other major bleeding in comparison to warfarin. Apixaban yields the most desirable result in comparison to others.

### The AHA updated 2019 guideline and the use of DOACS

The use of anticoagulants started in 1990s after the SPAF trial showed warfarin as the gold standard in preventing stroke in AFib patients. However, warfarin has many adverse effects, such as bleeding complications and ischaemic strokes, owing to the narrow therapeutic margin. Numerous randomised trials of DOACs, including RE-LY, ENGAGE AF-TIMI 48, ARISTOTLE, and ROCKET AF, have shown favourable results both in systemic embolization and stroke risk reduction compared to warfarin.

The new guideline added edoxaban for people with AFib and a CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> ≥ 2, while warfarin, dabigatran, apixaban and rivaroxaban remained the same as the 2014 guideline [6]. If oral anticoagulation is indicated in patients, the 2019 AHA guideline recommends warfarin as the first line treatment for those with CrCl ≤ 15 ml/min or those undergoing dialysis, followed by apixaban as the second choice of DOAC [6]. The AHA 2019 guideline recommends reduced doses of apixaban for patients with GFR ≥ 15, use of dabigatran for CrCl 15–30 ml/min, rivaroxaban for GFR < 50 and finally edoxaban for GFR 15–50, with an increased CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>C</sub> score [6, 36].

The updated guideline suggests that there is no benefit in using dabigatran, edoxaban or rivaroxaban in ESRD or for patients on dialysis. Moreover, the use of dabigatran is labelled as harmful for those with a artificial heart valve, regardless of the kidney function [6, 29]. Most DOACs have been shown to be either superior or non-inferior to VKA in reduction of thrombo-embolism in patients with AFib [23, 32, 36]. A progressive meta-analysis is underway comparing individual DOACs to one another and it is expected to increase in the near future. DOACs such as rivaroxaban and dabigatran have shown promising results with a decreased risk of adverse renal outcome compared to warfarin in patients with AFib. There are limited studies on drug interaction with DOACs and therefore well-designed trials are required to evaluate bleeding risk and their efficacy [6]. Likewise with warfarin there are some commercial assays to measure DOAC serum levels, but there is no set reference range that could show a safe dosage in terms of efficacy in clinical outcome [6]. New studies led the AHA to recommend idarucizumab for the reversal of dabigatran and andexanet for rivaroxaban reversal in their 2019 updated guidelines Table I [6, 16].

### Conclusions

DOACs are increasingly used in patients with kidney disease because they are more convenient and have improved pharmacological properties, have rapid action and have fewer adverse effects compared to warfarin. Their growing use calls for better understanding of their phar-

macokinetics and pharmacodynamics in patients with declining GFR. The risks and benefits of the FDA approved and the off-label DOACs are different in CKD and ESRD patients. There is limited support with regards to efficacy and safety of DOACs in patients with  $\text{CrCl} \leq 30$  ml/min or ESRD, due to adverse outcomes and hospitalisation. Almost every study excluded patients on dialysis and with  $\text{CrCl} \leq 30$  ml/min. Thus, deciding on the most efficient and safe DOAC agent is difficult in these patients and warfarin is still the best agent in this population. Patients with complications of warfarin are recommended to use apixaban with a corrected dose. More data are required on dabigatran, edoxaban and rivaroxaban for those with ESRD and for those on dialysis.

## Disclosure

The authors report no conflict of interest.

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