# DOAC use in patients with chronic kidney disease

## An update

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**Keywords**

Atrial fibrillation, dialysis, anticoagulation, calcineurin-inhibitors

**Summary**

Direct oral anticoagulants (DOACs) are increasingly prescribed substances in patients with indication for effective anticoagulation. Patients with chronic kidney disease (CKD) have a high burden of cardiovascular risk and are more likely to develop atrial fibrillation (AF) than patients without CKD. Patients with mild to moderate CKD benefit from DOACs, especially when having intolerance to vitamin K-antagonists (VKA). DOACs may in some cases be considered in patients with rare renal disease and hypercoagulabilic state. DOACs are to a large extent eliminated by renal excretion. Since prospective randomised data in CKD patients are sparse, the decision for anticoagulative therapy is challenging especially in patients with severe renal impairment. The direct factor Xa-inhibitors are approved for use even in patients with an estimated glomerular filtration rate (eGFR) between 15 and 30 ml/min. Careful monitoring of renal function on a regular basis is essential before initiation and after start of DOAC, especially for patients at risk for acute renal failure (elderly, diabetics, patients with preexisting kidney disease). None of the DOACs is approved in CKD patients with end-stage-renal-disease (ESRD) with or without dialysis. DOACs are not recommended for kidney transplant patients under immunosuppression with calcineurin inhibitors. In these patients conventional therapy with VKA is the only option, which has to be monitored closely since it has potential adverse effects.

**Schlüsselwörter**

Vorhofflimmern, Dialyse, Antikoagulation, Calcineurin-Hemmer

**Zusammenfassung**

Die direkten oralen Antikoagulantien (DOAK) werden zunehmend häufiger bei Patienten mit einer Indikation für eine effektive Antikoagulation verordnet. Im Vergleich zu Patienten ohne chronische Nierenerkrankung (CKD) haben Patienten mit CKD ein höheres kardiovaskuläres Risiko und eine höhere Wahrscheinlichkeit, Vorhofflimmern zu entwickeln. Die Behandlung mit DOAK ist bei Patienten mit milder bis mäßiger CKD von Vorteil, insbesondere wenn eine Unverträglichkeit gegen Vitamin-K-Antagonisten (VKA) besteht. DOAK können in Einzelfällen auch bei Patienten mit seltenen Nierenerkrankungen und Hyperkoagulabilität eingesetzt werden. Die DOAK werden zu einem großen Teil renal eliminiert. Da prospektive, randomisierte Daten zu CKD-Patienten rar sind, ist die Entscheidung für eine Antikoagulation schwierig, insbesondere bei Patienten mit deutlich eingeschränkter Nierenfunktion. Die direkten Faktor-Xa-Hemmer sind auch bei Patienten mit einer geschätzten glomerulären Filtrationsrate (GFR) von 15 bis 30 ml/min zugelassen. Es ist jedoch notwendig, die Nierenfunktion vor und nach Beginn der DOAK sorgfältig und regelmäßig zu evaluieren, besonders bei Patienten mit einem höheren Risiko für ein akutes Nierenversagen (Ältere, Diabetiker, Patienten mit bekannter Nierenerkrankung). Kein DOAK ist bei CKD-Patienten mit terminaler Nierenerkrankung, ob mit oder ohne Dialysetherapie, zugelassen. DOAK sind nicht empfohlen bei nierentransplantierten Patienten, die unter Immunsuppression mit Calcineurin-Hemmern stehen. Bei diesen Patienten ist die konventionelle Therapie mit VKA die einzige Möglichkeit und muss aufgrund potenziell unerwünschter Nebenwirkungen engmaschig kontrolliert werden.

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## Introduction

Chronic kidney disease (CKD) is a well known and independent risk factor for many cardiovascular diseases and death (1). Epidemiologic data from the US Medicare cohort show an overall CKD prevalence of about 14 % and the prevalence of any cardiovascular disease is about twice as high for those with compared to those without CKD (69.8 versus 35.2 %) (2) (▶Fig. 1). CKD is classified by decreased glomerular filtration rate (GFR) and/or stage of albuminuria. Currently five different stages of GFR (CKD 1–5) and three stages of albuminuria (A1–3) are defined (▶Tab. 1). Albuminuria stage 2 e.g. an albumin-creatinine-ratio (ACR) of

30–300 mg/g is the earliest sign of glomerular renal damage and already an independent risk factor for cardiovascular death as well as end stage renal disease (3). Atrial fibrillation (AF) and stroke is much more frequently observed in patients with CKD 1–5 with and without dialysis. Interestingly, proteinuria is also an independent risk factor for AF. Therefore many CKD patients have a need for effective anticoagulation.

## Atrial fibrillation and stroke prevention

Kidney disease leads to activation of the renin-angiotensin-aldosterone and the sympathetic nervous system. In addition, impaired kidney function triggers cardiac inflammatory processes which may lead to atrial fibrillation. Data from the Atherosclerosis Risk in Communities (ARIC)-cohort with more than 10 000 patients demonstrated that mild albuminuria A2 (ACR 30–299 mg/g), severe albuminuria A3 (ACR ≥ 300 mg/g) as well as CKD stage 4 with an estimated GFR (eGFR) of 15–29 ml/min are independent risk factors for AF. In this cohort, patients with eGFR < 30 ml/min and ACR > 300 mg/g had the highest risk for AF (hazard ratio 13.1) (4). Patients with chronic or paroxysmal AF have an up to 5-fold increased risk for ischemic stroke (5, 6). Studies in patients with CKD or with end-stage renal disease (ESRD) have shown that in the presence of AF the risk for stroke is more than 9-fold higher (7, 8). The one-year mortality was twice as high among hemodialysis patients with AF in the United States compared to those without (39 versus 19 %), and this increased risk was constant from 1992 to 2006 (9).

To determine individual risk for ischemic stroke the $CHADS_2$-Score or the $CHA_2DS_2$-VASc-Score are commonly used. Unfortunately studies to validate those scores excluded more advanced CKD and ESRD with or without dialysis. Interestingly, in the ROCKET-AF and ATRIA trial cohorts renal dysfunction (creatinine clearance < 60 ml/min) was a strong additional risk factor for stroke and systemic embolism (10). Each 10 ml reduction of creatinine clearance increased risk by 8.5 %. Considering the common comorbidities many if not most of the older CKD patients with AF will achieve at least 2 points in $CHA_2DS_2$-VASc-score and will therefore have an indication for vitamin K-antagonist (VKA)-therapy.

While the benefit of anticoagulation strategies to prevent stroke in AF patients with CKD stage 1–4 is not questioned, there is some controversy whether anticoagulation with VKA in CKD 5 and dialysis patients may be associated with more adverse events including ischemic stroke compared to patients without any therapy (11).

> It is worth noting that Phenprocoumon, which is the principally used VKA in Germany, is contraindicated in severe stages of CKD, while this does not apply to Warfarin, which is the mainly used VKA in the majority of studies.

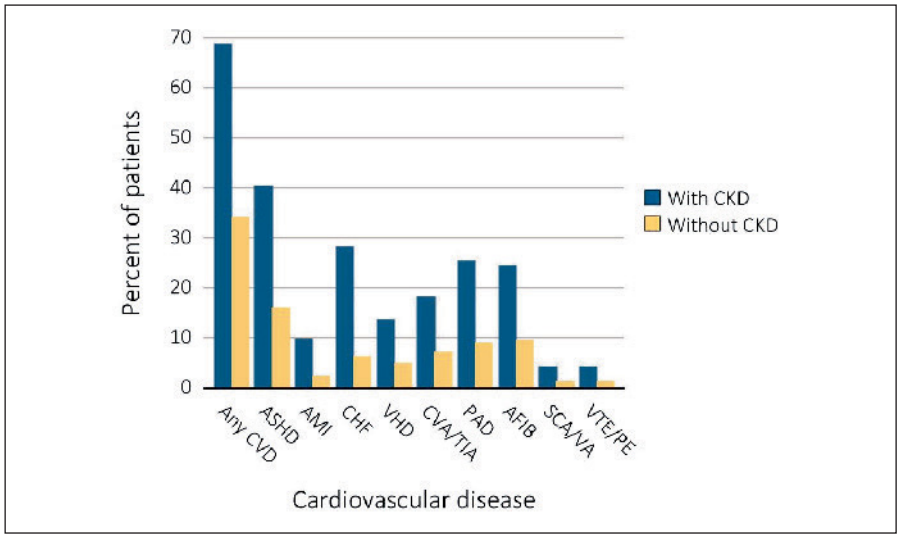


**Fig. 1** Cardiovascular disease in patients with or without CKD, 2013 (United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, 2016 [2]).

*Data Source to Figure 1:*

Special analyses, Medicare 5 % sample. Patients aged 66 and older, alive, without end-stage renal disease, and residing in the U.S. on 12/31/2013 with fee-for-service coverage for the entire calendar year. Totals of patients for the study cohort: N = 1 238 888; with CKD = 132 840; without CKD = 1 106 048. Abbreviations: AFIB: atrial fibrillation; AMI: acute myocardial infarction; ASHD: atherosclerotic heart disease; CHF: congestive heart failure; CKD: chronic kidney disease; CVA/TIA: cerebrovascular accident/transient ischemic attack; CVD: cardiovascular disease; PAD: peripheral arterial disease; SCA/VA: sudden cardiac arrest and ventricular arrhythmias; VHD: valvular heart disease.

*Notice: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.*

**Tab. 1** Stages of chronic kidney disease according to GFR in ml/min.

| stages of CKD, GFR (ml/min) | | | | | albuminuria stages, description and range (mg/g) | | |
|---|---|---|---|---|---|---|---|
| G 1 | G 2 | G 3 | G 4 | G 5 | A1 | A2 | A3 |
| > 90 | 60–89 | 30–59 | 15–29 | < 15 | < 10–29 | 30–299 | > 300 |

CKD: chronic kidney disease; GFR: glomerular filtration rate

Unfortunately, there are no randomized, prospective studies in CKD 5 or dialysis patients.

CKD and hemodialysis patients have an increased bleeding risk which is further elevated by oral anticoagulation therapy. Poor INR-control under VKA-therapy is associated with higher risk for ischemic as well as hemorrhagic events (12). Despite this fact patients on VKA are only 60 % of time in therapeutic range (13). In addition, dialysis patients suffer from uremic thrombocytopathy. Thus, initiation of VKA in CKD patients requires intensive monitoring especially in the first 30 days of treatment to avoid major bleeding (14). To assess major bleeding risk the use of the HAS-BLED–score is well etablished. In HAS-BLED CKD is a risk factor, but dialysis patients had not been included in those bleeding-risk-studies.

> Almost every dialysis patient scores 3 points in HAS-BLED, which would be associated with an estimated risk of 3.7 major bleedings per 100 patient years (15).

Not surprisingly some observational studies with dialysis patients and AF could not find clinical benefit in patients with warfarin therapy despite anticoagulation therapy by VKA, probably due to an increased risk of bleeding (16–18). As a consequence of this findings, the 2011 Kidney Disease: Improving Global Outcomes (KDIGO)-guidelines do not recommend VKA therapy for stroke prevention in dialysis patients with AF (19). But there are some positive observational data, i.e. in a large Swedish cohort with more than 300 000 patients with AF, most patients with renal failure had lower rates for ischemic as well as hemorrhagic stroke with warfarin therapy compared to patients without therapy (7). In contrast to KGIDO, the American Heart Association/American College of Cardiology/Heart Rhythm Society-guidelines from 2014 recommend warfarin therapy for patients with ESRD and AF with $CHA_2DS_2$-VASc-score of minimum 2 points (20).

Notably, a large Danish registry has evaluated the clinical net benefit of antithrombotic strategies in all patients with AF discharged from hospital between 1997 and 2011. They showed that high-risk CKD patients with AF ($CHA_2DS_2$-VASc≥2) including patients with renal replacement therapy benefit from warfarin treatment with respect to mortality and stroke prevention (21). This is in contrast to results of the Canadian study in 1626 dialysis patients older than 65 years and discharged with AF from hospital, which demonstrated no reduction in stroke incidence but higher bleeding risk (17).

> The controversial results of these observational studies are probably due to different patient care in the respective countries and differences of data collection quality.

Thus, prospective randomized studies testing different anticoagulation therapies in dialysis patients with AF are urgently needed.

## Pulmonary embolism and deep vein thrombosis

Pulmonary embolism is a serious complication of deep vein thrombosis with high in-hospital mortality (22). CKD is associated with hypercoagulability due to different hemostatic disturbances, e.g. rising levels of factor VIII and von Willebrand factor in decreasing kidney function (23, 24), so not surprisingly patients with ESRD or CKD of other stages are at increased risk for developing venous thrombosis with pulmonary embolism (25, 26). Besides that, diagnosis of pulmonary embolism in patients with impaired renal function is often difficult, since many of those patients have elevated D-dimers even without any thrombosis (27).

On the one hand, patients with kidney disease have higher risk for recurrent thromboembolic events and mortality (28) as compared to normal renal function and should be treated with anticoagulants urgently. But on the other hand those patients are more likely to have severe bleeding, especially under VKA (see above) or low molecular heparins like enoxaparin (29). Because most low molecular heparins will cumulate when renal function decreases, some are not approved in CKD stages 4–5. Special attention to more preferable substances and dose adjustment in CKD patients along with close monitoring of therapy are important.

Initial therapy with DOACs in pulmonary embolism requires a loading phase (21 days for rivaroxaban, 7 days for apixaban) or initial therapy with heparins (5 days before applicating dabigatran or edoxaban). Thus, close monitoring of kidney function to avoid complications due to overtherapy is recommended (see also [66]).

## Nephrotic syndrome and other rare kidney diseases

In primary kidney diseases alterations of the glomerular filter often lead to high-rate proteinuria with nephrotic syndrome. The most common diseases are membranous nephropathy and focal segmental glomerulosclerosis. Due to renal loss of albumin and other coagulation factors, patients with nephrotic syndrome are at increased risk for thromboembolic events (30), including pulmonary and renal vein thrombosis. Especially patients with membranous nephropathy seem to have a higher incidence of spontaneous vascular thrombosis and therefore a need for prophylactic anticoagulation (31). The KDIGO guidelines (32) recommend effective anticoagulation with VKA in patients with nephrotic proteinuria when serum albumin is below 2.0–2.5 g/dl and additional thrombosis risk factors are present until serum albumin rises to above 3 g/dl. Recently it was shown that patients with primary membranous nephropathy and nephrotic syndrome are also at increased risk for arterial thrombotic complications leading to cardiovascular events exceeding that of ESRD (33).

Antiphospholipid syndrome (APS) is an autoimmune disease associated with a high risk for vascular thrombosis and miscarriages. APS can als occur in systemic lupus erythematodes with or without renal impairment. Patients with APS are recommended for effective anticoagulation, mainly with VKA (34).

> Due to uncertainty for optimal INR range as well as VKA-interactions with other medication and food with implicit risk for recurrent thrombotic but also bleeding events (35), therapy with alternative anticoagulants might be considered, especially in patients with CKD.

Tab. 2 Dose recommendations for DOACs in atrial fibrillation according to phase III clinical trials of DOAC.

| | stages of CKD (GFR in ml/min) | | | | | |
|---|---|---|---|---|---|---|
| | I (> 90) | II (60–89) | III[a] (50–59) | III[b] (30–49) | IV (15–29) | V (< 15) |
| **dabigatran** | 2 × 150 mg | 2 × 150 mg | 2 × 150 mg | consider 2 × 110 mg | no approval | no approval |
| **rivaroxaban** | 1 × 20 mg | 1 × 20 mg | 1 × 20 mg | 1 × 15 mg | 1 × 15 mg | no approval |
| **apixaban** | 2 × 5 mg | 2 × 5 mg | 2 × 5 mg<br>consider** 2 × 2.5 mg | 2 × 5 mg<br>consider** 2 x 2.5 mg | use with caution: 2 × 5 mg | no approval |
| **edoxaban** | 1 × 60 mg* | 1 × 60 mg | 1 × 60 mg | 1 × 30 mg | 1 × 30 mg | no approval |

* if GFR > 95 ml/min: edoxaban should not be used
** if: creatinine ≥ 1.5 mg/dl and age > 80 years or weight < 60 kg

Furthermore, dialysis patients sometimes require therapy with anticoagulants because of dysfunction of dialysis access, e.g. thrombosis of central venous catheters or recurrent thrombosis of dialysis fistula. As mentioned above, anticoagulant therapy in dialysis patients is still challenging, despite its specific indication.

## Use of DOAC in AF

Since 2011 DOACs are an established therapy in AF patients. Besides the direct thrombin-inhibitor dabigatran the orally available direct factor-Xa inhibitors rivaroxaban, apixaban and edoxaban are therapeutical options in non-valvular AF (6). All DOAC studies showed non-inferiority for ischemic stroke risk compared to warfarin therapy while having less intracranial bleeding events. Of all DOACs only the direct thrombin-inhibitor dabigatran in a dose of 2 × 150 mg was superior in preventing ischemic stroke compared to warfarin.

### Use of DOAC in CKD patients

All DOACs are partially eliminated by the kidney. Therefore dose adjustment is needed in patients with CKD (▶Tab. 2). In this regard it is important to know that renal function can be estimated by different calculation formulas. The most commonly applied calculation is made by the Cockroft-Gault formula (36), which was used in almost all DOAC studies. This formula estimates creatinine clearance using patients age and weight:

- creatinine clearance (ml/min) = ([140 – age] × weight) / (72 × creatinine$_{serum}$); with correction factor 0,85 in women.

In contrast to the Cockroft-Gault formula other widespread formulas used by laboratories are CKD-EPI-formula (Chronic Kidney Disease Epidemiology Collaboration) (37) and Modification of Diet in Renal Disease (MDRD) formula (38), which estimate GFR and not creatinine clearance.

> The obtained values for staging of CKD may differ significantly between the formulas used. Some formulas do not consider age but race and may either under- or overestimate GFR. It is important to remember that serum creatinine levels have to be stable when using estimating formulas (39) to avoid wrong dose adjustment especially when using DOACs.

All direct factor-Xa inhibitors are approved for use in CKD stages 1–4 with a GFR of 15 ml/min, while Dabigatran only has approval for use in CKD stages 1–3 with GFR of 30 ml/min in Europe.

The working group „Heart-Kidney" of the German Cardiac Society and the German Society of Nephrology recently recommended to take a critical look before using DOACs in patients with CKD stage 4 (GFR 15–29 ml/min) and to prefer VKA for those patients due to sparse data. Additionally the authors conclude, that left atrial appendage occlusion instead of anticoagulative therapy may be an alternative for some patients with AF and severe CKD including dialysis patients with higher bleeding risk (40).

### Dabigatran

Dabigatran has a renal clearance of about 80 % and due to a relatively low protein-binding (35 %) it can be partially removed by dialysis (41). Thus, hemodialysis is an important tool to remove dabigatran in severe bleeding events. In the RE-LY study dabigatran was tested in a higher (2 × 150 mg) and a lower (2 × 110 mg) dose in comparison to warfarin in 18 113 patients with AF.

Both dabigatran groups were at least equal to warfarin in protecting from ischemic stroke and systemic embolism. The higher dose group was even better than warfarin (Hazard ratio 0.66; 95 % CI: 0.53–0.82), while lower rates of intracranial bleedings were observed in both dabigatran groups (42). In another study the rate of major bleeding was compared between dabigatran and warfarin with respect to kidney function. This study showed that major bleeding occured more often in dabigatran group when GFR fell below 50 ml/min (43).

> So dose adjustment to 2 × 110 mg dabigatran is strongly recommended in patients with GFR 30–50 ml/1.73 m² and with higher bleeding risk and patients of age > 80 years.

In RE-LY 3505 patients had eGFR <50 ml/min/1.73 m², but patients with an eGFR <30 ml/min/1.73 m² had been excluded. Dabigatran has no approval in CKD stages 4–5 (GFR <30 ml/min/1.73 m²) in Europe. However, the FDA (US Food and Drug Administration) has approved a lower dose of 2×75 mg in patients with CKD stage 4. This approval was only based on pharmacological data (44, 45), since prospective data in this cohort do not exist.

## Rivaroxaban

In the multicenter ROCKET-AF study 14264 patients with AF were either treated with 20 mg rivaroxaban (with dose reduction to 15 mg in patients with eGFR 30–49 ml/min) or with warfarin. Rivaroxaban was non–inferior to warfarin with respect to ischemic strokes and major bleeding. While more gastrointestinal bleeding occured in the rivaroxaban group, intracranial hemorrhage was less frequent as compared to the warfarin group (46). Approximately 21 % of the study cohort (2950 patients) had an eGFR 30–50 ml/min, while patients with GFR <30 ml/min had been excluded. Rivaroxaban has a renal clearance of about 35 %. With decreasing renal function an increase in plasma rivaroxaban levels up to 1.6-fold have been observed (46).

> ESC guidelines do not recommend rivaroxaban in patients with eGFR <30 ml/min (47, 53). However, rivaroxaban 15 mg once daily is approved for CKD patients with an eGFR down to 15 ml/min, but it should be used with caution in those patients. Dose adjustment due to age or low body weight is not needed.

In a recent subgroup analysis of ROCKET-AF 9292 (73.7 %) patients had stable and 3320 (26.3 %) had worsening renal function throughout the study period defined by a reduction in CrCl ≥20 % on treatment. Patients on rivaroxaban with worsening renal function had lower rates of stroke or systemic embolism compared to warfarin patients (1.54 versus 3.25 events per 100 patient years) with no difference in bleeding events (48). This is an interesting finding, since physicians tend to switch therapy in patients on DOAC with increasing creatinine levels due to fear of severe side-effects. This study suggests that those patients may instead benefit from staying on rivaroxaban therapy.

## Apixaban

The ARISTOTLE-study investigated the effects of the factor Xa-inhibitor apixaban (5 mg twice a day) compared to warfarin in 18201 patients with AF. Primary endpoints were ischemic or hemorrhagic stroke or systemic embolism (49). Dose adjustment down to 2.5 mg twice daily was done in patients with creatinine >1.5 mg/dl and age >80 years or body weight <60 kg. Apixaban has a renal clearance of about 27 %. In ARISTOTLE trial, 16.5 % of patients had a GFR <50 ml/min (50). Patients with eGFR <25 ml/min were excluded, but still 137 patients in the apixaban group and 133 in warfarin group had a GFR <30 ml/min.

Apixaban patients had 21 % lower rates of ischemic stroke compared to warfarin patients. Major bleeding events were also less frequent. Apixaban patients had 0.33 % intracranial hemorrhages per year whereas warfarin patients had 0.88 % per year. A subgroup analysis of ARISTOTLE study showed that patients with impaired renal function have even lower rates of stroke, major bleeding and mortality when taking apixaban compared to warfarin patients. This effect seemed to be mostly observed in patients with eGFR <50 ml/min (51).

> A meta-analysis of 40145 patients compaired bleeding risk of apixaban to other anticoagulation therapy. Patients with mild CKD had lower bleeding events with apixaban, while patients with severe CKD had similar bleeding risk compaired to warfarin, heparin or aspirin (52). Apixaban is not approved in patients with GFR <15 ml/min.

## Edoxaban

The ENGAGE-AF TIMI 48 trial is the largest trial to compare a direct factor Xa-inhibitor with warfarin in AF. The study with 21105 patients and a median follow-up of 2.8 years compared 60 mg edoxaban once daily vs. 30 mg edoxaban vs. warfarin. Edoxaban has a renal clearance of about 50 % and is a substrate of P-glycoprotein. Patients with eGFR <30 ml/min were excluded from the study. 1302 patients with eGFR 30–50 ml/min or weight <60 kg or use of P-glycoprotein-inhibitors like cyclosporine, verapamil or quinidone were given 30 mg edoxaban once daily.

The study showed non-inferiority of edoxaban compared to warfarin with respect to ischemic strokes and major bleeding events (53). In addition patients in edoxaban group with CKD stages 3–4 (eGFR 30–50 ml/min) even had a benefit for bleeding events when compared to warfarin group.

In a recent subgroup analysis of ENGAGE-AF TIMI 48 trial the efficacy and safety of edoxaban dependent on renal function was studied. Patients with an eGFR <50 ml/min did not differ from patients with eGFR >50 ml/min with respect to ischemic strokes or systemic embolism. In this study also hemorrhagic events did not differ in both groups. Edoxaban showed non–inferiority compared to warfarin group, independent of renal function. Only patients with very high eGFR >95 ml/min showed less prevention of thromboembolic events when treated with edoxaban compared to the warfarin group (HR 1.36; 95 % CI: 0.88–2.10) (54).

> Taking this into account, edoxaban therapy should be avoided in patients with high-normal renal function (GFR >95 ml/min) and AF. Edoxaban is not approved in CKD stage 5 (GFR <15 ml/min).

## Use of DOAC in CKD 5 and patients with renal replacement therapy

None of the new DOACs is allowed for therapy in patients with CKD 5 (eGFR <15 ml/min) or patients on dialysis in Europe. Therefore, renal function has to be assessed and monitored carefully before initiation of and also during DOAC therapy. Monitoring of renal function during therapy is especially important in patients with high risk for acute renal failure including acute on chronic renal failure and/or dehydration. A simplified formula to assess

Tab. 3 Absorption and metabolism of DOAC (modified after [18]).

| | bioavailability | protein binding | renal clearance | CYP3A4 involvement | P-glycoprotein involvement | intake with food |
|---|---|---|---|---|---|---|
| **dabigatran** | 3–7 % | 35 % | 80 % | no | yes | not necessary |
| **rivaroxaban** | 66 % (100 % with food intake) | > 90 % | 35 % | yes | yes | yes |
| **apixaban** | 50 % | > 85 % | 27 % | < 4 % | yes | not necessary |
| **edoxaban** | 62 % | > 50 % | 50 % | yes | yes | not necessary |

monitoring intervals when GFR is below 60 ml/min may be as follows:

- eGFR / 10 = interval in months (55).

Despite non-approval, there is evidence that even dialysis patients are increasingly being treated with DOACs. In a cohort study of 29 977 hemodialysis patients about 5.9 % of anticoagulated patients with AF got dabigatran or rivaroxaban. Those patients had a higher risk for bleeding events compared to warfarin (56), although dabigatran can be effectively removed by hemodialysis (57). Despite lack of efficacy or safety data for apixaban in ESRD patients, the FDA has allowed its use in hemodialysis patients with full dose of 2 × 5 mg. Remarkably, this allowance is based on pharmacological data obtained in only 8 dialysis patients (58). There are no prospective outcome data in this special population. This appears puzzling, since there are reports of fatal bleeding in dialysis patients treated with apixaban (59).

Prospective randomised studies are underway in Germany to investigate outcomes of dialysis patients with AF treated with apixaban or VKA (AXADIA-AFNET 8, ClinicalTrials.gov Identifier: NCT02933697).

### Betrixaban

The fourth oral factor Xa-inhibitor is underway. Betrixaban has no approval of use yet. In a phase 3 study with in-hospital patients with severe illness and risk for deep vein thrombosis, it appeared to be the first DOAC with a significantly better outcome compared to conventional therapy with enoxaparin (60). Study results for betrixaban in patients with AF or other thromboembolic risks and renal impairment are of great interest but are still to come.

## DOACs in kidney transplant patients – potential interactions with calcineurin-inhibitors

There are no prospective data for DOACs in kidney transplant patients. Even after successful transplantion these patient have a reduced eGFR. The calcineurin-inhibitors (CNIs) cyclosporine and tacrolimus are used in almost all renal transplant patients as baseline immunosuppression to prevent organ rejection. CNIs are inhibitors of Cytochrom-P (CYP)-enzymes and the effluxtransporter P-glycoprotein. Thus, CNIs inhibit degradation of all DOACs to a certain extent. Furthermore, transplant patients are likely to use comedication, e.g. antifungal treatment such as ketoconazole, which also has severe effects on DOAC metabolization. Cyclosporine itself is metabolized by CYP3A4 as well as by P-glycoprotein, whereas tacrolimus is metabolized by hepatic and to a lower amount by intestine enzyme CYP3A4.

> Due to unpredictable interactions with elevation of DOAC concentrations and the lack of prolonged observational studies in patients with CNI-therapy, we do not recommend the use of DOAC in kidney transplant patients.

- Dabigatran: Dabigatran and its active metabolite dabigatran etexilat are not metabolized by Cytochrom-P450-system and have no effect on CYP3A4. Therefore no drug interactions due to CYP3A4 have to be expected. However, dabigatran etexilat is a substrate of the effluxtransporter P-glycoprotein, so simultaneous therapy with P-glycoprotein-inhibitors such as CNIs will elevate dabigatran levels significantly. Therefore, strong P-glycoprotein inhibitors like cyclosporine, ketoconazole and dronedarone are contraindicated while using dabigatran. Tacrolimus use in dabigatran patients is not recommended (▶Tab. 3).
- Rivaroxaban: 66 % of oral rivaroxaban is metabolized. Half of the metabolites are excreted by the kidneys, the other half by feces. 33 % of the unmetabolized rivaroxaban is directly eliminated by the kidneys (active tubular secretion). Rivaroxaban is metabolized via CYP3A4, CYP2J2 and CYP-independent mechanisms. It is a substrate of P-glycoprotein. Use of strong inhibitors of CYP3A4 and P-glycoprotein as cyclosporine, is not recommended (61), moreover there is no pharmacological data of CNI use and plasma levels of rivaroxaban. Rivaroxaban itself will increase CNI-trough levels substantially (62). Nothing is known about long-term effects on transplant or patient outcome.
- Apixaban: Apixaban is metabolized by CYP3A4 and P-glycoprotein. Use of apixaban and strong inhibitors of CYP3A4 and P-glycoprotein like cyclosporine is not recommended (62), due to lack of pharmagological data. CNI- and apixaban-levels will be influenced by each other.
- Edoxaban: Edoxaban is metabolized by hydrolysis, conjugation or oxidation via CYP3A4/5 (< 10 %) and is a substrate of P-glycoprotein. In a study with 28 vol-

Tab. 4 Peak and through levels of DOAC, recommendations to last intake before risk-interventions according to CKD (modified after [55]).

| | plasma level | | low-risk intervention (e.g. endoscopy with biopsy) | | | | | high-risk intervention (e.g. kidney biopsy, ESWL) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | peak | through | stages of CKD (GFR in ml/min) | | | | | stages of CKD (GFR in ml/min) | | | | |
| | | | I-II (> 80) | II-III[a] (50–80) | III[b] (30–49) | IV (15–29) | V (< 15) | I-II (> 80) | II-III[a] (50–80) | III[b] (30–49) | IV (15–29) | V (< 15) |
| **dabigatran** | 2 h after ingestion | 12 h after ingestion | ≥ 24 h | ≥ 36 h | ≥ 48 h | n.i. | n.i. | ≥ 48 h | ≥ 72 h | ≥ 96 h | n.i. | n.i. |
| **rivaroxaban** | 2–4 h after ingestion | 24 h after ingestion | ≥ 24 h | ≥ 24 h | ≥ 24 h | ≥ 36 h | n.i. | ≥ 48 h | ≥ 48 h | ≥ 48 h | ≥ 48 h | n.i. |
| **apixaban** | 1–4 h after ingestion | 12 h after ingestion | ≥ 24 h | ≥ 24 h | ≥ 24 h | ≥ 36 h | n.i. | ≥ 48 h | ≥ 48 h | ≥ 48 h | ≥ 48 h | n.i. |
| **edoxaban** | 1–2 h after ingestion | 24 h after ingestion | ≥ 24 h | ≥ 24 h | ≥ 24 h | ≥ 36 h | n.i. | ≥ 48 h | ≥ 48 h | ≥ 48 h | ≥ 48 h | n.i. |

CKD: chronic kidney disease; GFR: glomerular filtration rate; n.i.: not indicated; ESWL: extracorporal shockwave lithotripsy

untary participants with normal kidney function once daily use of cyclosporine 500 mg and edoxaban drug levels were measured during a 24 hour period. Due to a rise of edoxaban blood levels, the dose of edoxaban had to be reduced to 30 mg with assumed drug levels (63). The use of cyclosporine in edoxaban patients is not a contraindication but should be done with great caution.

## Handling of DOAC in CKD patients before interventions with bleeding risk

In patients with CKD stage 3 (GFR 30–59 ml/min) or in elderly patients (> 75 years) on DOAC renal function has to be evaluated at least 2 times a year. Acute illness often transiently affects renal function (infections, acute heart failure, start or change of antihypertensive medication, contrast-media, etc), especially in older patients and also patients with CKD.

> Therefore it is essential to inform patients on DOAC about situations with potential risks for worsening renal function and the need for timely reevaluation. This is especially important for DOACs with higher renal clearance.

In planning a surgical intervention bridging with low molecular weight heparin or heparin is not necessary in DOAC-treated patients. Plasma peak levels are reached within 2 hours after intake of DOAC, plasma through levels are reached after 12 hours for DOAC with twice daily intake while for DOAC with once daily intake it is reached after 24 hours (▶Tab. 4).

In patients with CKD stages 3–4 plasma half-lives of DOACs are significantly higher compared to patients with normal renal function, in case of dabigatran half-lives would more than double (▶Table 5).

> Thus, CKD patients with need for surgical interventions may have to stop DOACs for a longer period of time than patients with normal renal function.

For patients with GFR < 80 ml/min and procedures with „minor bleeding risk" (e.g. endoscopy with tissue biopsy) or with „major bleeding risk" (e.g. kidney biopsy, prostate operation, any abdominal surgery, e.g. kidney transplantation) last intake of the anti-factor Xa-inhibitors should be ≥ 24 up to ≥ 48 h, and last intake of dabigatran should be or ≥ 36 h up to ≥ 96 h before surgical intervention (▶Tab. 4). For most surgical interventions, full dose anticoagulation should be restarted between 48 and 72 h after the procedure if the risk for embolism is also tolerable.

### Laboratory monitoring

Despite the fact that patients on DOACs do not need routinely monitoring of coagulation parameters there may be such a need in some patients at risk for severe bleeding, such as patients with CKD and severe interaction with other medication or urgent need for surgical intervention.

INR testing is not suitable for interpretation of anticoagulative effect of DOACs. Quantitative testing of plasma levels of DOACs is possible, for example with He-

Tab. 5 Estimated half times of different DOAC in chronic kidney disease stages (modified after [55]).

| | stages of CKD (GFR in ml/min) | | | | |
|---|---|---|---|---|---|
| | I-II (> 80) | II-III[a] (50–80) | III[b] (30–49) | IV (15–29) | V (< 15) |
| **dabigatran** | 12–17 h | 17 h | 19 h | 28 h | no data |
| **rivaroxaban** | 5–9 h (young)<br>11–13 (elderly) | 8.7 h | 9 h | 9.5 h | unsure |
| **apixaban** | 12 h | 14.6 h | 17.6 h | 17.3 h | unsure |
| **edoxaban** | 10–14 h | 8.6 h | 9.4 h | 16.9 h | unsure |

CKD: chronic kidney disease; GFR: glomerular filtration rate

moclot® for dabigatran (64). Chromogenic and drug-specific testing is available for the different anti-factor Xa inhibitors (65) but not widely spread, so physicians have to check availability in their laboratories.

While coagulation monitoring last intake of DOAC has to be considered since test results are altered with prolonged half-life of DOACs in CKD and also depend on whether maximum effect (peak levels) or trough levels of DOACs are requested. In order to examine whether patients with DOACs have accumulated drug levels it is more useful to take the blood sample just before planned next intake of DOAC.

## Summary

All DOACs are approved substances for use in patients with CKD stage 1–3 (eGFR > 30 ml/min) and AF or pulmonary embolism. Rivaroxaban, apixaban and edoxaban may also be used in patients with CKD stage 4 (eGFR between 15–30 ml/min), but careful monitoring of kidney function during the maintenance therapy is necessary.

On the one hand, there is lacking evidence for the efficacy and safety of DOACs in patients with ESRD, renal replacement therapy and kidney transplantation. But on the other hand there is no clear evidence for use of VKA in dialysis patients with AF. With exception of edoxaban in combination with cyclosporine, none of the DOACs is approved in transplant patients. There is an urgent need of prospective studies in this field.

### Conflict of interest

The authors declare that there are no conflicts of interest.

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