DOAC use in patients with chronic kidney disease

An update

S. Kücükköylü; L. C. Rump
Department of Medicine, Division of Nephrology, University of Düsseldorf

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.

Korrespondenzadresse
Univ.-Prof. Dr. med. Lars Christian Rump
Department of Medicine, Division of Nephrology, University of Düsseldorf
Moorenstr. 5
40225 Düsseldorf
Tel: 0049–211–81–17726
Fax: 0049–211–81–17722
E-mail: christian.rump@med.uni-duesseldorf.de

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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.

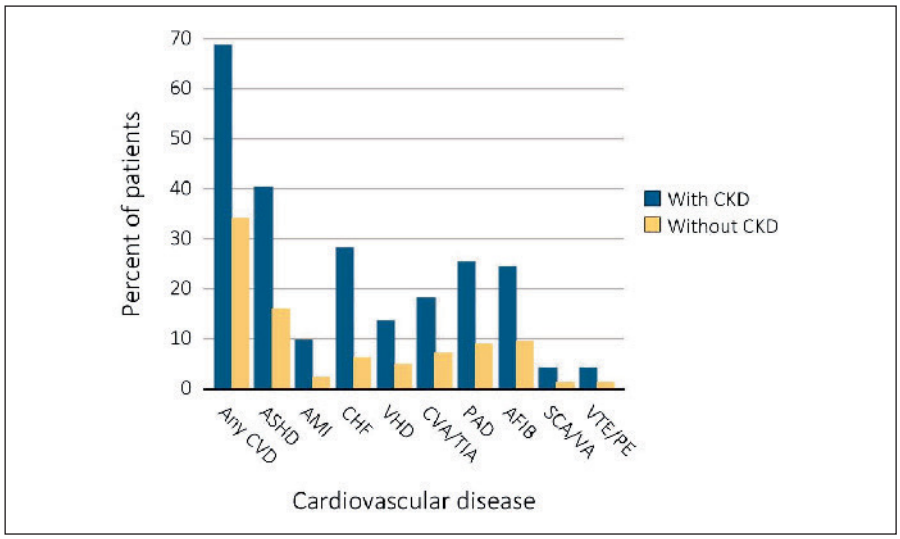

Fig. 1 Cardiovascular disease in patients with or without CKD, 2013 (United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, 2016 [2]).

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 consider** 2 × 2.5 mg	2 × 5 mg 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 14 264 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 18 201 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 40 145 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 21 105 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 co-medication, 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.

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) 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

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-

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.

References

1. Kucukkoylu S and Rump LC. [Renal insufficiency and cardiovascular diseases]. Internist 2012; 53: 791–801.
2. Saran R, Li Y, Robinson B et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kid Dis 2016; 67: S1–305.
3. Levey AS, de Jong PE, Coresh J et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80: 17–28.
4. Alonso A, Lopez FL, Matsushita K et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011; 123: 2946–2953.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983–988.
6. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016; 18: 1609–1678.
7. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2015; 36: 297–306.
8. Vazquez E, Sanchez-Perales C, Garcia-Garcia F et al. Atrial fibrillation in incident dialysis patients. Kidney Int 2009; 76: 324–330.
9. Winkelmayer WC, Patrick AR, Liu J et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. JASN 2011; 22: 349–357.
10. 10.Piccini JP, Stevens SR, Chang Y et al., Committee RAS and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation 2013; 127: 224–232.
11. Wizemann V, Tong L, Satayathum S et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010; 77: 1098–1106.
12. Mearns ES, White CM, Kohn CG et al. Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: a meta-analysis and meta-regression. Thromb J 2014; 12: 14.
13. Ansell J, Hollowell J, Pengo V et al. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). J Thromb Thrombol 2007; 23: 83–91.
14. Jun M, James MT, Manns BJ et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ 2015; 350: h246.
15. Yang F, Chou D, Schweitzer P et al. Warfarin in haemodialysis patients with atrial fibrillation: what benefit? Europace 2010; 12: 1666–1672.
16. Chen JJ, Lin LY, Yang YH et al. Anti-platelet or anti-coagulant agent for the prevention of ischemic stroke in patients with end-stage renal disease and atrial fibrillation – a nation-wide database analyses. Int J Cardiol 2014; 177: 1008–1011.
17. Shah M, Avgil Tsadok M, Jackevicius CA et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014; 129: 1196–1203.
18. Chan KE, Giugliano RP, Patel MR et al. Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF. J Am Coll Cardiol 2016; 67: 2888–2899.
19. Herzog CA, Asinger RW, Berger AK et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011; 80: 572–586.
20. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64: e1–76.
21. Bonde AN, Lip GY, Kamper AL 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: 2471–2482.
22. Anderson FA, Jr., Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Int Med 1991; 151: 933–938.
23. Wattanakit K, Cushman M. Chronic kidney disease and venous thromboembolism: epidemiology and mechanisms. Curr Op Pulm Med 2009; 15: 408–412.
24. Ocak G, Vossen CY, Lijfering WM et al. Role of hemostatic factors on the risk of venous thrombosis in people with impaired kidney function. Circulation 2014; 129: 683–691.
25. Mahmoodi BK, Gansevoort RT, Naess IA et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. Circulation 2012; 126: 1964–1971.
26. Cook D, Crowther M, Meade M et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med 2005; 33: 1565–1571.
27. Lindner G, Funk GC, Pfortmueller CA et al. D-dimer to rule out pulmonary embolism in renal insufficiency. Am J Med 2014; 127: 343–347.
28. Tsai J, Abe K, Boulet SL et al. Predictive accuracy of 29-comorbidity index for in-hospital deaths in US adult hospitalizations with a diagnosis of venous thromboembolism. PloS one. 2013; 8: e70061.
29. Hoffmann P, Keller F. Increased major bleeding risk in patients with kidney dysfunction receiving enoxaparin: a meta-analysis. Eur J Clin Pharmacol 2012; 68: 757–765.
30. Rankin AJ, McQuarrie EP, Fox JG et al. Venous Thromboembolism in Primary Nephrotic Syndrome – Is the Risk High Enough to Justify Prophylactic Anticoagulation? Nephron 2017; 135: 39–45.
31. Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. Kidney Int 1994; 45: 578–585.
32. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines – application to the individual patient. Kidney Int 2012; 82: 840–856.
33. Lee T, Derebail VK, Kshirsagar AV et al. Patients with primary membranous nephropathy are at

high risk of cardiovascular events. Kidney Int 2016; 89: 1111–1118.
34. Negrini S, Pappalardo F, Murdaca G et al. The antiphospholipid syndrome: from pathophysiology to treatment. Clin Exp Med 2016 [Epub].
35. Crowl A, Schullo-Feulner A, Moon JY. Warfarin monitoring in antiphospholipid syndrome and lupus anticoagulant. Ann Pharmacother 2014; 48: 1479–1483.
36. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.
37. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Int Med 2009; 150: 604–612.
38. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Int Med 1999; 130: 461–470.
39. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ et al. Creatinine Clearance Is Not Equal to Glomerular Filtration Rate and Cockcroft-Gault Equation Is Not Equal to CKD-EPI Collaboration Equation. Am J Med 2016; 129: 1259–1263.
40. Schlieper G, Schwenger V, Remppis A et al. [Anticoagulation in patients with chronic kidney disease : Recommendations from the working group „Heart-Kidney" of the German Cardiac Society and the German Society of Nephrology]. Internist 2017; 58: 512–521.
41. Maegdefessel L, Spin JM, Azuma J et al. New options with dabigatran etexilate in anticoagulant therapy. Vascular health and risk management. 2010; 6: 339–349.
42. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
43. Hijazi Z, Hohnloser SH, Oldgren J et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation 2014; 129: 961–970.
44. Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. J Clin Pharmacol 2012; 52: 119S-125S.
45. Lehr T, Haertter S, Liesenfeld KH et al. Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation. J Clin Pharmacol 2012; 52: 1373–1378.
46. Patel MR, Mahaffey KW, Garg J et al. and Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–891.
47. Camm AJ, Lip GY, De Caterina R et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719–2747.
48. Fordyce CB, Hellkamp AS, Lokhnygina Y et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF. Circulation 2016; 134: 37–47.
49. Granger CB, Alexander JH, McMurray JJ et al. Committees A and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–992.
50. Goto S, Zhu J, Liu L, et al. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Am Heart J 2014; 168: 303–309.
51. Hohnloser SH, Hijazi Z, Thomas L et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012; 33: 2821–2830.
52. Pathak R, Pandit A, Karmacharya P et al. Meta-analysis on risk of bleeding with apixaban in patients with renal impairment. Am J Cardiol 2015; 115: 323–327.
53. Giugliano RP, Ruff CT, Braunwald E et al. and Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093–2104.
54. Bohula EA, Giugliano RP, Ruff CT et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation 2016; 134: 24–36.
55. Heidbuchel H, Verhamme P, Alings M et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015; 17: 1467–1507.
56. Chan KE, Edelman ER, Wenger JB et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 2015; 131: 972–979.
57. Khadzhynov D, Wagner F, Formella S et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. Thromb Haemost 2013; 109: 596–605.
58. Wang X, Tirucherai G, Marbury TC et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol 2016; 56: 628–636.
59. Kufel WD, Zayac AS, Lehmann DF et al. Clinical Application and Pharmacodynamic Monitoring of Apixaban in a Patient with End-Stage Renal Disease Requiring Chronic Hemodialysis. Pharmacotherapy 2016; 36: e166-e171.
60. Cohen AT, Harrington RA, Goldhaber SZ et al. and Investigators A. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med 2016; 375: 534–544.
61. Wannhoff A, Weiss KH, Schemmer P et al. Increased levels of rivaroxaban in patients after liver transplantation treated with cyclosporine A. Transplantation 2014; 98: e12–13.
62. Vanhove T, Spriet I, Annaert P et al. Effect of the direct oral anticoagulants rivaroxaban and apixaban on the disposition of calcineurin inhibitors in transplant recipients. Ther Drug Monit 2017; 39: 77–82.
63. Parasrampuria DA, Mendell J, Shi M et al. Edoxaban drug-drug interactions with ketoconazole, erythromycin, and cyclosporine. Brit J Pharmacol 2016; 82: 1591–1600.
64. Dale BJ, Chan NC, Eikelboom JW. Laboratory measurement of the direct oral anticoagulants. Br J Haematol 2016; 172: 315–336.
65. Samuelson BT, Cuker A, Siegal DM et al. Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants: A Systematic Review. Chest 2017; 151: 127–138.
66. AWMF-Leitlinie 2015: http://www.awmf.org/uploads/tx_szleitlinien/065–002l_S2k_VTE_2016–01.pdf

