Anticoagulation in patients with impaired renal function and with haemodialysis

Anticoagulant effects, efficacy, safety, therapeutic options

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Summary

Patients with impaired renal function are exposed to an increased risk for bleeding complications depending on the amount of the anticoagulant eliminated by the kidneys. The elimination of unfractionated heparins, vitamin K antagonists and argatroban is only minimally influenced by a reduced renal function. Low-molecular weight heparins, fondaparinux, danaparoid, hirudins and non-vitamin K antagonist oral anticoagulants (NOAC) cause a variably increased bleeding risk in renal impairment. Dose reductions are recommended for all of these anticoagulants in renal impairment, some are even contraindicated at certain levels of renal impairment. Their benefit over the conventional anticoagulants is preserved if renal dosing is employed. For end-stage renal disease patients specific treatment regimens are required.

Zusammenfassung

Patienten mit einer eingeschränkten Nierenfunktion sind einem erhöhten Blutungsrisiko durch Antikoagulanzien ausgesetzt, das von der Nierenausscheidung des Antikoagulanz abhängt. Die Elimination von unfraktioniertem Heparin, Vitamin-K-Antagonisten und Argatroban wird nur geringfügig von der Nierenfunktion beeinflusst. Niedermolekulare Heparine, Fondaparinux, Danaparoid, Hirudin und Nicht-Vitamin-K-Antagonist orale Antikoagulanzien (NOAK) sind mit einem erhöhten Blutungsrisiko bei abnehmender Nierenfunktion verbunden. Dosisreduktionen sind für alle diese Antikoagulanzien erforderlich in Abhängigkeit von der Nierenfunktion, einige sind bei schwerer Nierenfunktionstörung sogar kontraindiziert. Der Benefit gegenüber konventionellen Antikoagulanzien bleibt bei renaler Dosisanpassung bestehen. Für Hämodialysepatienten liegen spezifische Behandlungsregime vor.

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Vitamin K antagonists (VKA), unfractionated heparins (UFH), low-molecular weight heparins (LMWH), non-vitamin K antagonist oral anticoagulants (NOAC), hirudins, and as specific drugs argatroban and danaparoid are used in the prevention of venous thromboembolism (VTE) in postoperative and non-operative medicine, for treatment of acute VTE and prevention of recurrent events, prevention and treatment of stroke and other systemic emboli in patients with non-valvular atrial fibrillation (NVAF), following artificial heart valve replacement therapy and in specific indications of acute coronary syndromes(1).

> All these drugs have specific limitations in various diseases with impairment of renal function applying to the majority of them (2).

VKA are characterized by a delayed onset of action, need for regular laboratory monitoring to guide dose adjustments, considerable inter-individual variability in pharmacokinetics and pharmacodynamics, interactions with drugs, food and acute illnesses. Minor, major or fatal haemorrhages, coumarin induced hepatitis, allergic skin reaction of minor or severe intensity, coumarin induced skin necrosis, hair loss and other side effects may occur during therapy at any time and in most instances without relation to the intensity of anticoagulation (3). In order to overcome their limitations NOAC were developed and are approved for prevention of embolic

events in patients with non-valvular atrial fibrillation (NVAF) and for treatment of acute venous thromboembolism and prevention of its recurrent events(4).

UFH and LMWH are proven to effectively prevent thromboembolism in many indications including extracorporeal circulation with UFH and haemodialysis (5). They are administered by intravenous or subcutaneous applications and UFH requires laboratory monitoring to adjust the activated partial thromboplastin time (aPTT) in a therapeutic range of a 2 to 3 fold prolongation. LMWH improved anticoagulant therapy compared to UFH in many indications due to body weight adjusted or fixed dosing without laboratory guided dose adjustment and less frequently occurring side effects. Side effects include heparin-induced thrombocytopenia (HIT) type I or type II, haemorrhage, cutaneous allergic reactions, heparin-induced skin necrosis, decrease of antithrombin, heparin-resistance, hair loss, increase of liver enzymes (6).

Hirudins are approved in specific interventions for treatment of acute coronary syndromes and danaparoid as well as argatroban for anticoagulation of patients suffering from HIT type I or II. All of these anticoagulants have to be given systemically and require laboratory guided dose adjustment. For hirudins and argatroban therapeutic aPTT values range from a 2 to 3 fold prolongation; danaparoid needs to be adjusted to an anti-factor Xa level between 0.4 and 0.8 units/ml. Side effects to hirudins include allergic reactions specifically after subcutaneous administration, development of antibodies, and relevant accumulations observed in patients with impaired renal function (7). Bleeding complications are increased during simultaneous antiplatelet therapy (8).

Fondaparinux is a synthetic pentasaccharide with high affinity to antithrombin and an elimination half-life of about 17 hrs following fixed dose subcutaneous administration. Its efficacy and safety are similar or superior in several indications compared to LMWH. It does not bind to platelet factor 4 (PF4) like UFH and LMWH, which builds a complex of UFH or LWMH with a PF4 tetramer for generation of heparin-PF4 antibodies. Other side effects relate to bleeding complications which occur less frequently compared to LMWH (9). The relevant pharmacological data of the anticoagulants are summarized (►Tab. 1).

Impaired renal function

The liver and kidneys are the most important sites of drug excretion, which is expressed as clearance (renal and non-renal). Absorption, distribution, metabolism, and excretion can all be altered in renal impairment. Renal excretion is the major pathway for elimination of both unchanged drugs and their metabolites. Drugs may be excreted by glomerular filtration and/or renal tubular secretion. Glomerular filtration of a molecule depends on molecular weight, charge (anionic, neutral, or cationic) and degree of plasma protein binding. Small (<10 000 daltons), neutral or cationic, and weakly protein-bound drugs pass easily through the glomerular membrane (10).

Renal function, evaluated by the glomerular filtration rate (GFR), declines with age, and studies have shown a mean decrease by 0.75 ml/min/year exposing a large inter-individual variation (11). The most widely used classification of renal

Tab. 1   Relevant pharmacological characteristics of anticoagulants; modified from ref. (10)

anti-coagulant	elimination	half-life with normal renal function	monitoring	antidote	dose adjustment in severe renal impairment
UFH	• RES • renal (minimal)	30–150 min after IV administration	aPTT, anti-Xa, ACT	protamine	• low dose: no monitoring • medium and high dose: monitoring recommended
LMWH	• mainly renal • RES (minimal)	2–8 h after SC administration	anti-Xa	protamine partially effective	yes, differences between LMWHs
r-Hirudin	• mainly renal • hepatic (minimal)	• ~40 min after IV, • ~120 min after SC injection	aPTT, ECT	none	yes, according aPTT values
bivalirudin	• proteolytic cleavage ~80% • renal ~20%	~25 min after IV administration	ACT, aPTT	none	yes, according ACT or aPTT values
argatroban	hepatic 100% (CYP3A4)	40–50 min after IV administration	aPTT, ACT, ECT	none	dose adjustment according aPTT values
danaparoid	mainly renal	18–28 h after SC administration	anti-Xa	none	yes, plasma anti-Xa monitoring
fondaparinux	renal >80%	17–21 h after SC administration	anti-Xa	none	drug not recommended in patients with severe renal impairment
VKA	hepatic 100% (CYP2C9, VCOR system)	~36–42 h	INR	vitamin K, PPSB, FFP	careful dose titration recommended in patients with severe renal impairment

RES: reticulo endothelial system; ACT: activated clotting time; ECT: ecarin clotting time; CYP: cytochrom P; VCOR: vitamin K epoxid reductase; PPSB: prothrombin complex concentrate; FFP: fresh frozen plasma

impairment has been published by the American National Kidney Foundation (►Tab. 2) (12).

As bleeding complications may occur independently of the intensity of anticoagulation additional risk factors such as sex, age, concomitant diseases may influence their occurrence. In the present review the focus lies on the interaction of the individual anticoagulants with renal function to give outlines on anticoagulant preferences in certain thrombotic indications in relation to different severities of renal impairment.

Vitamin K antagonists
Renal insufficiency and haemodialysis

VKA are renally eliminated by only 10–15%, they are extensively metabolized by the liver. The occurrence of multimorbidity increases with increasing age including age related decrease of renal function. Liver function also deteriorates with age, but to a lesser extent than renal function. Decreases of the lean body-mass and in total body water lower the volume of distribution additionally aggravated by a decrease of albumin concentration in blood. These functional changes cause a higher variation of INR values in the elderly compared to younger patients. As a consequence bleeding and – if variability leads to under-treatment – thrombotic events increase with age (13). The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study evaluated the risk profile of warfarin-associated haemorrhage. Anaemia and severe renal disease (e.g., glomerular filtration rate <30 ml/min or dialysis-dependent) were independent variables with the highest values to predict haemorrhagic risk of patients treated with warfarin (14).

If the bleeding risk in elderly patients is regarded as high or very high during anticoagulation with VKA, LMWH may be considered as alternative for anticoagulation (15).

Therapeutic consequences for patients with impairment of renal function including those on haemodialysis should be considered for therapy with VKA:

Tab. 2
Classification of renal impairment; National Kidney Foundation according GFR category (G) (ml x 1.73 m²) (12)

glomerular filtration rate		terms
category	ml/min × 1.73 m²	
G1	>90	normal or high
G2	60–89	mildly decreased
G3a	45–59	mildly to moderately decreased
G3b	30–44	moderately to severely decreased
G4	15–29	severely decreased
G5	<15	kidney failure

- decreased dose of VKA in elderly both for initiation and maintenance
- increased sensitivity to VKA during intercurrent diseases and concomitant medications including dose changes
- delayed normalization of INR following cessation of therapy and establishment of therapeutic INR after re-starting of VKA therapy
- consideration of higher sensitivity to drug-drug interactions involving the CYP450 2C9 isoenzyme
- increase of bleeding complications with concomitant administration of platelet inhibitors and non-steroidal anti-inflammatory drugs (NSAIDS).

Heparins, low-molecular weight heparins
Renal insufficiency

Data from animal studies and healthy volunteers suggest that, with heparin dosages <100 U/kg, clearance of UFH occurs mainly via the RES and the endothelium (16). Only at higher doses, some intact heparin molecules are recovered in the urine. The half-life of UFH appears to be slightly prolonged, by a factor of approximately 1.5, in patients with severe renal impairment. Early reports describe elimination of heparins by 30% as inactive desulfated compound. Research of the past decades showed that renal elimination of sulfated polysaccharides such as heparins increases at lower molecular weight; thus, renal elimination is maximal for the comparably small pentasaccharide fondaparinux. LMWHs dalteparin, certoparin, tinzaparin and enoxaparin differ considerably with respect to molecular weight and pharmacokinetics (17–19). For enoxaparin a 50%

reduction of dose is required at a creatinine clearance of <30 ml/min and fondaparinux is contraindicated at this stage of renal impairment. Laboratory guided dosing resulted in longer time of anti-factor Xa activity being in the therapeutic range compared to conventional fixed dosing (20).

Meta-analyses confirmed the increased risk of bleeding for patients with renal insufficiency receiving LMWH (21, 22). Twelve studies including almost 5000 patients found major bleeding in 5% of patients with CrCl < 30 ml/min, compared to 2.4% in patients with CrCl > 30 ml/min (odds ratio = 2.2, p = 0.013). In the ExTRACT-TIMI 25 trial the enoxaparin dose was reduced for age ≥75 years (0.75 mg/kg SC BID) and with CrCl < 30 ml/min (1 mg/kg once daily). In the IRIS trial (Innohep in Renal Insufficiency Study), including patients above 70 years of age with acute deep vein thrombosis, no significant accumulation was detected with age, body-weight or creatinine clearance for tinzaparin given at fixed doses subcutaneously versus aPTT adjusted intravenous UFH. The mean anti-FXa activity did not differ significantly between the patients who experienced clinically relevant bleeding and those who did not in both groups of patients (23). The study was terminated earlier due to a higher mortality rate of patients treated with tinzaparin without finding risk factors for this outcome (24). UFH does not rely on renal elimination and remains an option particularly for treatment of patients with CrCl < 30 ml/min(25, 26).

Haemodialysis

To overcome the side effects of UFH, several LMWH, dalteparin, enoxaparin, fraxiparin and tinzaparin were developed and

creatinine clear-ance ml/min	half-life (h)	bolus dose (mg/kg bw)	infusion rate (mg/kg bw x h)
>80	1.0	0.5	0.2
60–80	2.4	0.4	0.15
45–59	4.0	0.2	0.075
30–45		0.2	0.045
15–29	12.2	0.2	0.0025
<15	>15	0.2	in most cases avoid or stop infusion

Tab. 3
Key pharmacokinetic parameters and the dosing of hirudin in relation to impairment of renal function (8)

finally approved for anticoagulation during haemodialysis. The advantages of LMWH over UFH are a lower incidence of bleeding, lower incidence of thrombocytopenia, and improvement of hyperlipidaemia (27). Dosing differs between the LMWHs as well as the anti-factor Xa levels to be obtained during or at the end of dialysis. A meta-analysis identified no difference in bleeding events or thrombosis of the extracorporeal circuit when LMWH was compared with UFH. LMWH and UFH were given at effective doses according to anti-factor Xa levels of 0.2 to 0.4 IU/ml 2 h after initiation of dialysis (28) corresponding to current clinical practice recommendations for anticoagulation with UFH (29). The interpretation of the reports from the literature and the experimental data demonstrate that UFH and some LMWH are predominantly cleared from the circulation without major renal impact.

In summary, the advantages of LMWH over UFH in patients with renal insufficiency undergoing haemodialysis are the following:
- single bolus injection for a 4-h-haemodialysis,
- no laboratory dose adjustment,
- lower incidence of HIT, osteopenia and other side effects.

Hirudins, danaparoid, argatroban
Renal impairment, haemodialysis

Hirudins are polypeptides isolated from the saliva of medicinal leeches (Hirudo medicinalis) with a molecular weight of about 6500 Dalton which specifically in-hibit thrombin and its precursor meizo-thrombin. Its recombinant variants are lepirudin and desirudin. The elimination half-life is about 60 min following intravenous administration requiring laboratory guided dose adjustment to maintain the aPTT prolonged to the 2 to 3-fold of normal. Hirudins are eliminated unaltered almost completely by renal excretion; renal dosing may lead to substantial dose reductions to only 5% of the normal dose in patients with end stage renal disease (30) (►Tab. 3). r-hirudins may induce allergy and antibodies (31).

Danaparoid is a sulphated polysaccharide composed of chondroitinsulfate, heparansulfate, and contains about 5% of a LMWH fraction. It is given as intravenous infusion or subcutaneously at about 4000 IU per day to maintain the anti-factor Xa level in a range of 0.5 to 1.0 IU/ml. It is excreted predominantly by the liver and partially by the kidneys (see LMWH). As it contains LMWH and heparin-like compounds it may be ineffective or generate heparin-PF4 antibodies in about 15% of patients (31). Nevertheless, caution is required to treatment of patients with a reduced creatinine-clearance using danaparoid.

Argatroban is a synthetic small molecular weight thrombin inhibitor (MW about 500 Dalton) which requires intravenous infusion due to a half-life of about 1 h and an aPTT adjustment to a prolongation of 2 to 3 of the reference range. The anticoagulant is metabolised by the liver independently of renal function (32).

The clinical recommendations for the use of those anticoagulants mentioned in patients with renal insufficiency or haemodialysis can be summarized as follows:
- The thrombin inhibitors r-hirudins and argatroban have to be adjusted to prolong aPTT 2 to 3 fold of normal.
- Danaparoid requires dose adjustment to obtain factor Xa inhibition of 0.5 to 1.0 IU/ml (peak levels).
- The dose of r-hirudin, desirudin and bivalirudin has to be reduced to about 15% in renal insufficiency according to the aPTT.
- The dose of hirudins has to be reduced in patients on haemodialysis to about 7 mg subcutaneously before onset of

Tab. 4   Relevant pharmacological data of NOAC in humans

parameter		dabigatran	rivaroxaban	apixaban	edoxaban
prodrug		yes	no		
molecular weight		628	436	460	548
target		thrombin	factor Xa		
bioavailability		6–7%	80%	60%	50%
food effect		delays absorption		no	
dosing regimen		bid	od	bid	od
time to peak level (h)		1–3	2–4	1–3	1–2
plasma protein binding		35%	95%	85%	40–60%
elimination half life (h)		12–17	9–13	8–15	6–11
metabolism		• 80% renal • 20% liver	• 66% renal* • 33% liver	• 25% renal • 75% liver	• 35% renal • 65% liver
substrate	CPY	no	3A4, 2J2	3A4	
	P-gp	yes			

bid: twice daily; CYP: cytochrome P450; od: once daily; P-gp: P-glycoprotein; *1/3 active drug

dialysis depending on the prolongation of aPTT.

- The dose of danaparoid has to be reduced in renal impairment according to a therapeutic range to 0.4 to 0.8 IU/ml.
- Argatroban is eliminated predominantly by the liver and may be used without relevant dose reduction in patients with renal impairment according to a target aPTT of 2 to 3-fold prolongation.

NOAC

Renal impairment

The non-vitamin K antagonist oral anticoagulants (NOAC) dabigatran as thrombin inhibitor and rivaroxaban, apixaban and edoxaban as factor Xa inhibitors are approved for several clinical indications. The relevant pharmacological parameters of NOAC are shown (▶Tab. 4). There are important differences between these NOAC regarding their renal elimination: it is 80% for dabigatran and ranges from to 25 to 60% for the direct oral factor Xa inhibitors.

Thus, the elimination of NOAC variably decreases with decreasing renal function. Therefore, patients on treatment with NOAC and with impaired renal function may be exposed to an increased risk of bleeding due to drug accumulation (33).

Dabigatran

Dabigatran etexilate is a small synthetic molecule and is administered as an oral prodrug. It is rapidly converted in the liver through esterases via two intermediate metabolites to the active compound, dabigatran, which is a competitive, direct and reversible thrombin inhibitor. The parent drug has a low bioavailability of approximately 6.5%, and a low pH is required in order to achieve a good absorption, which is why the capsules containing dabigatran etexilate are micropellets around a tartaric core (34).

Renal excretion of unchanged dabigatran is the predominant elimination pathway, with about 80% of an intravenous dose being excreted unchanged in the urine. Under conditions of clinical studies, exposure to dabigatran was increased by renal impairment and correlated with the severity of renal dysfunction. The mean

Tab. 5 The ratio of patients with renal impairment over healthy subjects is shown for the maximal concentration (Cmax) and the area under the concentration time curve (AUC, ng x h/ml) after administration following a single oral administration of dabigatran (47)

parameter	renal impairment	ratio (90% CI)
Cmax (ng/ml)	mild	1.11 (0.61, 2.03)
	moderate	1.70 (0.93, 3.10)
	severe	2.12 (1.25, 3.59)
AUC (ng x h/ml)	mild	1.50 (0.78, 2.90)
	moderate	3.15 (1.63, 6.08)
	severe	6.31 (3.54, 11.25)

Cmax: maximal concentration; AUC: area under the curve

clearance of total dabigatran decreased from 62.9 ml/min in the healthy control group to 10.3 ml/min in subjects with severe renal impairment. The mean elimination half-life of dabigatran increased from 13.8 hours in healthy subjects to 16.6 hours, 18.7 hours and 27.5 hours in subjects with mild, moderate and severe renal impairment, respectively (▶Tab. 5).

Rivaroxaban

Rivaroxaban is a small molecule and acts as an oral, reversible, direct FXa inhibitor. It is rapidly absorbed, has a high bioavailability, and maximum plasma concentration is reached within 2–3 hours. After oral administration, it has an almost linear pharmacokinetic profile and a mean elimination half-life of 7–11 hours in young

healthy adults and of 11–13 hours in the elderly (35). Rivaroxaban has a dual mode of elimination, with approximately two-thirds of the dose undergoing degradation to inactive metabolites through CYP3A4 and CYP2J2 and through CYP-independent mechanisms with one-half of the metabolized drug being eliminated by renal excretion and the other half by hepatobiliar route. The final third of the dose is excreted unchanged through the kidneys (36).

The influence of renal function on rivaroxaban clearance is moderate, even in subjects with severe renal impairment. Decreased renal clearance leads to increased rivaroxaban plasma concentrations. AUC is increased by 44% in subjects with mild renal impairment, 52% in those with moderate renal impairment, and by 64% in those with severe impairment, compared with healthy controls (▶Tab. 6) (37).

A sub-analysis of the ROCKET trial reported on subjects with moderate renal insufficiency [CrCl 30–49 mL/min], in whom the dose of rivaroxaban was reduced from 20 to 15 mg daily (38). The principal safety endpoint (major and clinically relevant non-major bleeding) occurred more frequently in patients with renal insufficiency. However, there was no excess bleeding on both doses of rivaroxaban compared with warfarin. Of note, critical organ bleeding and fatal bleeding were less frequent with rivaroxaban which is consistent with the findings of the total study population of the ROCKET trial) (38). In the Japanese J-ROCKET AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention

Tab. 6 Pharmacokinetic parameters of rivaroxaban after the administration of a single 10 mg dose of oral rivaroxaban to healthy controls and subjects with mild, moderate and severe renal impairment (37)

parameter	healthy controls	renal impairment		
		mild	moderate	severe
(n = 8)		n = 8	n = 8	n = 8
CLCr (ml min⁻¹)	117.1 ± 29.3	66.5 ± 8.1	42.6 ± 5.0	22.2 ± 4.6
Cmax (mg l⁻¹)	172.3 (30.7)	217.5 (37.9)	206.2 (26.0)	232.2 (33.1)
CLR (l h⁻¹)	2.4 (46.5)	1.2 (29.2)	0.7 (33.1)	0.5 (40.4)
AUC ratio (90% CI) vs. healthy controls	–	1.44 (1.08, 1.91)	1.52 (1.15, 2.01)	1.64 (1.24, 2.17)

Abbreviations: see text and Tab. 5; CLR: renal clearance of drug; data given as geometric mean and % of coefficient of variation unless indicated differently

creatinine clearance (ml/min)	bleeding risk					
	dabigatran		rivaroxaban		apixaban	
	low	high	low	high	low	high
> 80	>24 h	> 48 h	> 24 h	> 48 h	> 24 h	> 48 h
50 – 80	> 36 h	> 72 h				
30 – 50	> 48 h	> 96 h				
15 – 30	contraindicated		> 36 h		> 36 h	
< 15	contraindicated					

Tab. 7
Recommendations of the European Heart Rhythm Association to stop anticoagulation with NOAC before a surgical intervention (48)

of stroke and Embolism Trial in Atrial Fibrillation) study, rivaroxaban 15 mg once daily was given to patients with creatinine clearance (CrCl) ≥ 50 ml/min (preserved renal function), and was reduced to 10 mg once daily in patients with CrCl 30–49 ml/min (moderate renal impairment). The safety and efficacy data on rivaroxaban 10 mg od vs. INR-adjusted warfarin were consistent with those in patients with normal renal function and moderate impairment treated with 15 mg od (39).

Plasma, serum and urine concentrations were determined under real life conditions during therapy with 20 mg rivaroxaban od. Mean concentrations of rivaroxaban in plasma samples were lower compared to serum samples using determination of the anti-factor Xa activity by chromogenic assays. The concentrations of rivaroxaban in urine were about 50-fold higher compared to plasma and serum levels due to the excretion of about 60% of the administered dose (40). No correlation between the plasma, serum or urine levels of rivaroxaban and the creatinine clearance of patients was found.

Apixaban

Apixaban is an oral, potent, reversible, direct, and highly selective inhibitor of the coagulation factor Xa, which plays a pivotal role in the clotting cascade by decreasing the conversion of prothrombin to thrombin. The oral bioavailability of apixaban is approximately 50%, and its elimination half-life is approximately 12 hours. Apixaban is eliminated by both renal and non-renal pathways, and is a substrate for the P-glycoprotein and breast cancer resistance protein transporters. Non-renal elimination pathways include metabolism by cytochrome P450 (CYP) enzymes, primarily CYP3A4. Renal excretion of apixaban accounts for approximately 27% of total clearance(41). Pharmacokinetic data in relation to renal function are not available.

In the ARISTOTLE trial comparing apixaban, a drug with low renal excretion, with VKA, patients with non-valvular atrial fibrillation impaired renal function seemed to have the greatest reduction in major bleeding with apixaban (42) as compared to other NOAC investigated for this indication.

Edoxaban

Edoxaban is one of several selective, direct, oral factor factor-Xa inhibitors binding to both free and to the prothrombinase complex bound factor Xa, thereby producing a dose-dependent decrease in thrombin generation(43). It reaches peak plasma concentrations in 1–2 hours (h) with a mean terminal elimination half-life of 8–10 h in healthy subjects and an oral bioavailability of 62%. It is eliminated through multiple pathways and a significant portion of systemically absorbed drug is eliminated via renal excretion (44). Metabolites are formed through hydrolysis with minor contribution by cytochromeP4503A. Strong P-glycoprotein (P-gp) inhibitors increase the exposition to edoxaban. P-gp are efflux transporters primarily expressed in the luminal membranes of epithelia of the small intestine, hepatocytes, and renal proximal tubules (45). Data on the influence of renal function on the pharmacokinetics are not available. Bleeding complications were not increased in patients treated with acute VTE and a creatinine clearance between 30 and 60 ml/min compared to normal renal function. However, many of these patients received a lower dose of edoxaban (46).

Conclusion

Based on the reviewed data (►Tab. 7) the following conclusion may be drawn for an adequate use of anticoagulants in patients with renal insufficiency:

- prophylaxis of VTE in postoperative and non-operative medicine with
  - normal or moderately (ClCr > 30ml/min) impaired renal function: LMWH, fondaparinux, UFH,
  - severely reduced renal function (ClCr < 30 ml/min): UFH or laboratory adjusted LMWH (peak aXa levels: <0.2 IU/ml)
- treatment of VTE or prevention of embolism in NVAF with
  - normal and moderately reduced (ClCr > 30 ml/min) renal function: NOAC or VKA, initiation with fondaparinux or LMWH according to marketing approval
  - severely reduced renal function (ClCr 15–30 ml/min): reduced doses of rivaroxaban and apixaban or VKA
  - end-stage renal disease (ClCr<15ml/min): VKA
- patients with unstable angina and normal renal functions: rivaroxaban and clopidogrel or dual platelet inhibitors (both regimens on top of aspirin)
- prevention of thrombotic occlusion of the dialysator equipment in haemodialysis: LMWH as bolus or dose adapted bolus and infusion of UFH
- patients with HIT (type I or type II) with normal or impaired renal function: dose adjusted i.v. r-hirudin, i.v. argatroban and iv. or s.c. danaparoid.

Conflict of interest

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