

## Direct oral anticoagulants: efficacy and safety in patient subgroups

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### Summary

Direct oral anticoagulants have recently emerged as an attractive choice for patients requiring anticoagulation treatment. They have a rapid onset of action and can be administered at fixed doses without the need for routine anticoagulation monitoring. They may present fewer interactions than warfarin but further experience is needed to assess the clinical significance of the interactions with cytochrome CYP3A and P-gp inhibitors/inducers. A higher rate of bleeding has been observed in association with antiplatelet agents or non-steroidal anti-inflammatory drugs. Their safety profile has not been sufficiently studied in the elderly, and in patients with liver disease or severe renal impairment. Dose adjustment is necessary in patients with moderate renal impairment and a higher bleeding rate has been observed in this subgroup, although not higher than with warfarin. The clinical settings that require monitoring of coagulation assays have not yet been specified. Reversal of their anticoagulant effect may be problematic in case of severe bleeding. Therefore, despite the obvious advantages of the direct oral anticoagulants, experience is still lacking for many patient subgroups in which they should be withheld awaiting more data.

**Key words:** *direct oral anticoagulants; apixaban; dabigatran; edoxaban; rivaroxaban; interactions; chronic kidney disease; elderly; monitoring*

### Introduction

Direct oral anticoagulants have recently emerged as an attractive choice for patients requiring long-term anticoagulation treatment. They act through direct and selective inhibition of either factor Xa (rivaroxaban, Xarelto<sup>®</sup>, apixaban, Eliquis<sup>®</sup> or edoxaban, Savaysa<sup>®</sup>) or thrombin (dabigatran, Pradaxa<sup>®</sup>) and are now referred to as direct oral anticoagulants (DOACs). They have a rapid onset of action, and offer the advantage to be administered at fixed doses without the need for routine anticoagulation monitoring [1].

DOACs were initially used for the prevention of venous thromboembolism (VTE) after total hip or knee replacement [2]. Large-scale clinical trials have recently been conducted expanding their indications to the treatment of VTE (BOTTICELLI, EINSTEIN-DVT, EINSTEIN-PE, RECOVER, AMPLIFY, HOKUSAI-VTE) [3–8], and stroke prevention in atrial fibrillation (AF) (RE-LY, ROCKET, ARISTOTLE and ENGAGE AF-TIMI 48) [9–12]. The efficacy and safety of DOACs were also evaluated for extended treatment of VTE with encouraging results [4, 13–14].

According to the recent clinical practice guidelines of the American College of Chest Physicians [15], dabigatran may be preferred for stroke prevention in AF rather than adjusted-dose vitamin K antagonist (VKA) therapy (grade 2B recommendation). The 2012 focused update of the European Society of Cardiology guidelines for the management of AF now recommends the DOACs as preferable to VKA in patients with non-valvular AF [16].

With their current and potential indications rapidly expanding, special attention is required to monitor the severe adverse effects of these new drugs, essentially in specific patient groups such as the elderly or patients with chronic kidney disease. This review aims to present current experience with the four oral direct anticoagulants which have reached or are reaching phase IV clinical development: rivaroxaban, apixaban, dabigatran and edoxaban.

### Main side effects

Bleeding episodes constitute the main adverse effects of the DOACs. Definition of bleeding events in the studies evaluating the DOACs follows the International Society on Thrombosis and Haemostasis (ISTH) criteria [17]. Major bleeding is commonly defined as clinically overt and associated with a decrease in the haemoglobin level of 20 g per litre or more, or if it led to transfusion of two or more units of red cells, was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. Table 1 summarises the frequency of major bleeding events in the most recent clinical trials evaluating the DOACs in the treatment of VTE and stroke prevention in AF [3–12].

In several of these large clinical trials, major bleeding events occurred less frequently in patients who received the DOACs in comparison to warfarin (EINSTEIN-PE, AMPLIFY, the 110 mg dabigatran arm in RE-LY, ARISTOTLE and ENGAGE AF-TIMI 48). In the ROCKET-AF study, critical or fatal bleeding events as well as intracranial haemorrhage were less frequent in the rivaroxaban treated patients. However, bleeding from the gastrointestinal (GI) tract occurred more frequently in the rivaroxaban group. Intracranial haemorrhage rate was also lower in apixaban treated patients in the ARISTOTLE trial, in rivaroxaban treated patients in the EINSTEIN-PE study and in edoxaban treated patients in the ENGAGE AF-TIMI 48 trial. In the RE-LY trial, there was a significantly lower rate of intracranial bleeding (0.30% vs 0.74% per year) but a significantly higher rate of gastrointestinal bleeding (1.51% vs 1.02% per year) with dabigatran at the 150mg bid dose compared with warfarin. It has been proposed that dabigatran preserves haemostatic mechanisms in the brain because it does not interfere with the formation of tissue factor-FVIIa complexes. The selectivity of major bleeding events in the GI tract may be due to local effects of unabsorbed dabigatran on diseased mucosa. On the other hand, unabsorbed warfarin cannot cause bleeding because it requires metabolism by hepatic enzymes to exert any anticoagulant effect [18].

A pooled analysis of the EINSTEIN trials demonstrated a statistically lower major bleeding rate with rivaroxaban (1.3%) compared with standard treatment (4.5%) in fragile patients (hazard ratio of 0.27, 95% confidence interval [CI] 0.13-0.54). Such a difference was not identified in nonfragile patients. Fragility was defined as the presence of at least one of the following criteria: age >75 years, calculated creatinine clearance <50 ml/min or body weight ≤50 kg. Recurrent VTE was more common in fragile than nonfragile patients. The effects on major bleeding rate and VTE recurrence were consistent across the specific components that defined the fragile population [19].

A recent meta-analysis warned against a higher risk of acute coronary events in patients receiving dabigatran [20]. Data from 30,514 participants in seven randomised controlled trials were examined. Dabigatran administration was associated with a modest increase of myocardial infarction or acute coronary syndrome (ACS) risk (odds ratio 1.33, 95% CI 1.03–1.71). However, the absolute risk difference was small (0.14–0.17%) yielding a number needed to harm of around 700. The observed effect might not be due to a dabigatran associated increase in the risk of ACS, but to the absence of the beneficial effects of the comparator therapy in patients receiving dabigatran. A differential antiplatelet use among treatment groups is highly improbable in randomised trials and is unlikely to explain this finding. Therefore, the eventual cardiac risk of dabigatran should be investigated further, especially in populations at high risk of ACS [20].

Post-marketing data are scarce for most of DOACs. In the months following the approval of dabigatran in the United States, an unusually high rate of bleeding incidents was reported via the FDA adverse events reporting system, leading the agency to issue a drug safety communication [21]. Further analysis of the data in the FDA database was reas-

suring with respect to bleeding and the high reporting rate was attributed to the novelty of the drug [21].

A recently published study on a nationwide cohort of AF in Denmark included 52,366 patients who were followed-up for 4 months. The adjusted risk of VTE was higher among dabigatran users who previously received VKA and may be due to poor compliance and unmeasured comorbidities. Bleeding risk increased in patients on dabigatran 110 mg compared with VKA but not among patients on dabigatran 150 mg. However, patients on dabigatran 150 mg were younger with a lower HAS-BLED score compared with patients on VKA or dabigatran 110 mg. A more cautious approach is recommended while switching patients on VKA to dabigatran treatment [22].

The RELY-ABLE study extended the follow-up of patients completing the RE-LY trial by an additional 2.3 years. Patients enrolled in this study were less likely to have had a stroke or a bleeding event during RE-LY. There was no significant advantage of the 150 over the 110 mg dose for the outcome of stroke or systemic embolism. The annual rate of major bleeding was higher for the 150 mg dose compared with the 110 mg dose. However, events were not adjudicated and data analysis was not with the intention to treat [23].

A recent study analysed all available case reports and single case series on bleeding complications in patients receiving rivaroxaban or dabigatran [24]. Haemorrhagic complications were more frequently reported with dabigatran. At least one risk factor (concomitant antiplatelet treatment or significant drug-drug interaction, renal impairment, age >80) was present in 24 out of the 28 reported cases.

In the RELY study, dyspepsia was more commonly reported in patients receiving dabigatran (11.3%) compared with warfarin (5.8%), and accounted for half of cases of dabigatran withdrawal. This frequent side effect should be taken into account in patients with dyspepsia history.

## Drug and food interactions

The absence of major and frequent pharmacokinetic interactions with other commonly administered drugs would be a significant advantage of the DOACs [1]. However, data with these agents are limited. Several clinically relevant drug interactions are awaited with strong inhibitors of both cytochrome P450 3A4 and P-glycoprotein (P-gp), but theoretical ones should also be considered and further evaluated [25].

Rivaroxaban and dabigatran are substrates of the P-gp, an efflux transporter of many commonly prescribed drugs. Significant drug-drug interactions are awaited with P-gp inducers and inhibitors (table 2) [26]. Rifampicin, a potent P-gp inducer, administered at the 600 mg dose once daily, reduced by 66% the area under the curve (AUC) of a dabigatran single dose [24]. Ketoconazole 400 mg and dronedarone 400 mg BID respectively increased dabigatran AUC by 138% and 170% [27].

Rivaroxaban and apixaban (but not dabigatran) are also metabolised by the cytochrome P450 (CYP) 3A4/5 enzyme. Ketoconazole 400 mg once daily and ritonavir 600mg twice daily increased rivaroxaban AUC by 2.6 fold

and 2.5 fold, respectively [28]. Therefore, the use of rivaroxaban is contra-indicated with protease inhibitors or azole antifungal agents (table 2). Apixaban is predominantly metabolised by CYP3A/5 with a minor involvement of CYP1A2. Ketoconazole doubled apixaban plasma concentrations in a phase I study [29]. Further studies assessing pharmacokinetic drug interactions between apixaban and CYP3A inhibitors/inducers are needed.

Drug-drug interactions altering the absorption of the DOACs have also been reported. Proton pump inhibitor administration reduces dabigatran bioavailability by 12.5% [30]. This effect may be due to decreased gastric acidity because dabigatran requires an acid pH for its absorption [9]. Omeprazole had no clinically significant interaction with rivaroxaban [31].

Following food consumption, the absorption of dabigatran is delayed but without significant clinical implications [28]. Rivaroxaban at the 15 and 20 mg doses should be taken with food because its absorption increases [32]. High fat meals had no effect on the apixaban bioavailability.

Caution flags have been raised concerning increasing bleeding risk associated with the co-administration of an anticoagulant with either a non-steroidal anti-inflammatory drug (NSAID) or antiplatelet agents. A higher rate of bleeding has been observed when these agents are co-administered with warfarin. A pooled analysis of the EINSTEIN DVT and PE studies showed an increased risk for major bleeding events during NSAIDs use compared with the major bleeding rate during nonuse of NSAIDs: HR of 2.56 (95% CI 1.21–5.39) for rivaroxaban treated patients and HR of 2.28 (95% CI 1.28–4.04) for enoxaparin-VKA treated patients [33]. For aspirin users (15% of patients), increase in major bleeding events was not significant either for rivaroxaban treated patients (HR of 1.50, 95% CI 0.63–3.61) or for enoxaparin-VKA treated patients (HR of 1.50, 95% CI 0.74–3.05) [33]. In the RE-LY study, use of antiplatelet agents (up to 38% of patients) was associated with increased risk of major bleeding events in each of the treatment groups. The relative increase was consistent whether patients were assigned to dabigatran or warfarin. Triple therapy, i.e., the association of dual antiplatelet therapy with anticoagulation, further increases bleeding risk. In the RE-LY trial, the risk of major bleeding seemed high-

er among patients who also received dual antiplatelet treatment (HR 2.31; 95% CI 1.79–2.98) than among patients who received only one antiplatelet agent (HR 1.60; 95% CI 1.42–1.82) [34]. Therefore, concomitant use of antiplatelet agents or NSAIDs in patients on DOACs should be limited to the minimum time necessary.

## Use in specific clinical settings

No studies have been conducted in specific patient groups. Existing data are derived from the large randomised phase III trials. However, statistically significant differences in *post hoc* subgroup analyses should be interpreted with caution, especially if there is no overall difference between the treatment groups.

### Elderly patients

Elderly people have a higher rate of kidney or liver disease and extremes in body weight compared with younger individuals. This association adds to the potential toxicity of DOACs for this patient subgroup. Their safety has not been sufficiently studied in elderly patients. Available evidence for efficacy and security outcomes with DOACs in elderly patients with AF is summarised in table 3.

A subgroup analysis of the RE-LY trial results demonstrated a significant interaction between treatment and age regarding major bleeding events [18]. The safety benefit of dabigatran was no longer observed in the >75 years age group. Both doses of dabigatran were associated with an increasing relative risk of major bleeding events with increasing age categories. The interaction between treatment and age concerned extracranial and gastrointestinal bleeding. Intracranial bleeding rates were lower in patients treated with dabigatran irrespective of age.

The pharmacokinetics and pharmacodynamics of different oral doses of rivaroxaban have been studied in healthy elderly patients. Rivaroxaban was well tolerated and had predictable anticoagulant effects in this age group. However, studied patients were aged 60–76 years (mean 66 years) and 59–74 years (mean 62 years) [35–36]. In the ROCKET-AF trial, stroke or systemic embolism and major bleeding events were more frequent in patients aged >75 regardless of the treatment group. The alleged benefit of rivaroxaban

**Table 1:** Major bleeding events in the clinical trials evaluating the direct oral anticoagulants in the treatment of venous thromboembolism and stroke prevention in atrial fibrillation.

Study	Time frame	Major bleeding events		HR (95% CI)
		DOAC	Standard treatment	
BOTTICELLI [3] (apixaban)	At 3 months (%)	0.8	0	N/A
Einstein Acute-DVT [4] (rivaroxaban)	3 to 12 months (%)	0.8	1.2	0.65 (0.33–1.30)
Einstein-PE [5] (rivaroxaban)	3 to 12 months (%)	1.1	2.2	0.49 (0.31–0.79)
RECOVER [6] (dabigatran)	At 6 months (%)	1.6	1.9	0.82 (0.45–1.48)
AMPLIFY [7] (apixaban)	At 6 months (%)	0.6	1.8	0.31 (0.17–0.55)
HOKUSAI-VTE [8] (edoxaban)	3 to 12 months (%)	1.4	1.6	0.84 (0.59–1.21)
RE-LY [9] (dabigatran 110 mg bid)	Per 100 patient-years	2.7	3.4	0.80 (0.69–0.93)
RE-LY [9] (dabigatran 150 mg bid)	Per 100 patient-years	3.1	3.4	0.93 (0.81–1.07)
ROCKET-AF [10] (rivaroxaban)	Per 100 patient-years	3.6	3.4	1.04 (0.90–1.20)
ARISTOTLE [11] (apixaban 5 mg bid)	Per 100 patient-years	2.1	3.1	0.69 (0.60–0.80)
ENGAGE AF-TIMI 48 [12] (edoxaban 60 mg qd)	Per 100 patient-years	2.8	3.4	0.80 (0.71–0.91)
ENGAGE AF-TIMI 48 [12] (edoxaban 30 mg qd)	Per 100 patient-years	1.6	3.4	0.47 (0.41–0.55)

bid = twice daily; DOAC = direct oral anticoagulant; N/A = not available; qd = once daily

The observed difference in the incidence of major bleeding events may be due to variable duration of intended treatment.

concerning intracranial haemorrhage is not identified in the >75 years age group [37].  
 In the ARISTOTLE study, stroke or systemic embolism and major bleeding events were more frequent in the patients aged ≥75 years compared with the <65 years age

group. This increase in the bleeding rate tended to be greater in warfarin treated patients than in apixaban treated patients, although the confidence intervals overlap [11]. No significant interaction was detected between age category

**Table 2:** Pharmacokinetic drug-drug interactions with direct oral anticoagulants and possible clinical consequences [26].

Molecules	P-gp inhibitors	P-gp inducers	CYP3A inhibitors	CYP3A inducers
	<b>Antiarrhythmic</b> amiodarone, dronedarone, diltiazem propafenone, quinidine, verapamil <b>Antibiotics</b> erythromycin, clarithromycin <b>Antidepressants</b> duloxetine, fluoxetine, paroxetine, reboxetine, sertraline <b>Antifungal</b> ketoconazole, itraconazole <b>Antihypertensive</b> irbesartan <b>Antiplatelet</b> dipyridamole <b>Antipsychotic</b> haloperidol, quetiapine <b>Antiviral</b> atazanavir, efavirenz, lopinavir, nelfinavir, ritonavir, saquinavir <b>Contraceptives</b> desogestrel <b>Immunosuppressive</b> ciclosporin <b>Growth factor inhibitors</b> erlotinib, nilotinib <b>Opioids</b> methadone <b>Proton pump inhibitors</b> lansoprazole <b>Statins</b> simvastatin <b>Vinca alkaloids</b> vinblastine	<b>Antimycobacterial</b> rifabutine, rifampicin <b>Antiepileptic</b> carbamazepine <b>Antiviral</b> nevirapine <b>Corticosteroids</b> dexamethasone St John's wort	<b>Antiarrhythmic</b> amiodarone, dronedarone, diltiazem, verapamil <b>Antibiotics</b> erythromycin, clarithromycin, roxithromycin, ciprofloxacin, doxycyclin <b>Antidepressants</b> fluoxetine, fluvoxamine, nefazodone, reboxetine <b>Antifungal</b> fluconazole, ketoconazole, itraconazole, miconazole, posaconazole, voriconazole <b>Antihypertensive</b> dihydralazine, nitrendipine <b>Antimycobacterial</b> isoniazide <b>Antipsychotic</b> quetiapine <b>Antiviral</b> atazanavir, darunavir, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapin, ritonavir, saquinavir <b>Contraceptives</b> desogestrel, ethinylestradiol, gestodene <b>Corticosteroids</b> methylprednisolone <b>H2 antagonists</b> cimetidine <b>Immunosuppressive</b> ciclosporin <b>Growth factor inhibitors</b> dasatinib, imatinib, nilotinib, sorafenib <b>Miscellaneous</b> grapefruit, curcuma, liquorice	<b>Alkylating agents</b> cyclophosphamide ifosfamide <b>Analgesics</b> metamizole <b>Antimycobacterial</b> rifabutine, rifampicin <b>Antiviral</b> efavirenz, etravirine, nevirapin <b>Antiepileptic</b> carbamazepine, phenytoin, phenobarbital, primidone, topiramate, oxcarbamazepine, felbamate <b>Anxiolytic</b> meprobamate <b>Corticosteroids</b> dexamethasone <b>Endothelin antagonists</b> bosentan <b>Miscellaneous</b> modafinil, ethanol, St John's wort
<b>Theoretical pharmacokinetic and clinical consequences</b>	Reduced elimination and increased toxicity (bleeding) of rivaroxaban, apixaban and dabigatran	Accelerated elimination and reduced efficacy of rivaroxaban, apixaban and dabigatran	Reduced elimination and increased toxicity (bleeding) of rivaroxaban and apixaban	Accelerated elimination and reduced efficacy (?) of rivaroxaban and apixaban

**Table 3:** Efficacy and safety of direct oral anticoagulants in elderly patients with atrial fibrillation.

Study		Age <75			Age ≥75		
		Stroke or systemic embolism (%/year)	Major bleeding (%/year)	Intracranial bleeding (%/year)	Stroke or systemic embolism (%/year)	Major bleeding (%/year)	Intracranial bleeding (%/year)
ROCKET-AF [10, 40]	Rivaroxaban	2.00	2.21–3.04	0.29–0.48	2.29	5.16	0.72
	Warfarin	2.10	2.16–3.34	0.62–0.75	2.85	4.47	0.81
RE-LY [9, 21]	Dabigatran 110 mg bid	1.32	1.89*	0.14*	1.89	4.43	0.37*
	Dabigatran 150 mg bid	0.90*	2.12*	0.26*	1.43*	5.10	0.41*
	Warfarin	1.43	3.04	0.61	2.14	4.37	1.00
ARISTOTLE [11]	Apixaban	1.00–1.25	1.17–1.99	0.28–0.31	1.56*	3.33*	0.43*
	Warfarin	0.86–1.73	1.51–2.82	0.35–0.81	2.19	5.19	1.29
ENGAGE AF-TIMI 48 [12]	Edoxaban 30 mg qd	1.71	1.23*	N/A	2.55	2.26*	N/A
	Edoxaban 60 mg qd	1.35	2.02*		1.91	4.01	
	Warfarin	1.48	2.62		2.31	4.83	

bid = twice daily; N/A = no data on intracranial haemorrhages in specific age groups available in the paper; qd = once daily  
 \* p <0.05 vs warfarin

and randomised treatment with respect to the efficacy outcome of stroke or systemic embolism.

In the ENGAGE AF-TIMI 48 trial, no statistically significant interaction was observed between treatment and age group concerning either stroke and systemic embolism or major bleeding events [12].

Limited data are available on VTE treatment trials with DOACs because the mean age of patients is much lower than in AF trials. Subgroup analyses by age for major bleeding events have not been published yet for dabigatran. A pooled analysis of both EINSTEIN trials suggested that rivaroxaban may be safer in patients >75 years old, although the interaction between age category and treatment was not statistically significant [38]. In the AMPLIFY trial, the safety benefit of apixaban persisted in the  $\geq 75$  years age group [7]. In the HOKUSAI-VTE trial, a trend favouring edoxaban efficacy was present in the  $\geq 75$  year age group. No interaction was identified between treatment and age regarding major bleeding events [8].

### Chronic kidney disease

Renal excretion is the predominant elimination pathway for dabigatran. Its half-life increases from 12 to 17 hours in healthy individuals to 13 to 23 hours in patients with moderate renal impairment (creatinine clearance [CrCl] 30–50 ml/min) and 22 to 35 hours in those with severe renal impairment (CrCl <30 ml/min) [39].

The response to a single 150 mg dose of dabigatran etexilate was studied in patients with impaired renal function. Renal insufficiency prolonged dabigatran elimination, resulting in increased plasma concentrations and overall exposure. Compared with healthy subjects, there was a 1.5, 3.2 and 6.3 fold increase in dabigatran exposure with mild, moderate and severe renal impairment, respectively. In uremic patients, 50mg was administered at the beginning of a 4 hour dialysis session. The mean fractions of the drug removed by dialysis were 62% at 2 hours and 68% at 4 hours [40].

A two-compartment disposition model was constructed to describe the pharmacokinetics of dabigatran in 9,522 patients from the RE-LY trial [30]. Among the other studied covariates (age, sex, heart failure, ethnic subgroup), renal function had the most important effect on dabigatran plasma concentrations. A decrease in creatinine clearance from 100 to 80 ml/min resulted in an 11% increase in systemic exposure. A decrease from 50 to 30 ml/min increased exposure by 50%. Patients with creatinine clearance less than 30 ml/min were not included in the study.

In the RE-LY trial, the risk of bleeding increased with decreasing creatinine clearance. This increase was more pronounced in patients receiving dabigatran 110 mg twice daily (relative risk-RR of 3.5 in patients with creatinine clearance <50 ml/min compared with patients with creatinine clearance >80 ml/min) than warfarin (respective RR of 2.3) [18].

The FDA approved dabigatran 75 mg twice daily in patients with severe renal impairment (defined as CrCl between 15 and 30 ml/min) [41]. This dose was derived from a phase I trial studying the pharmacokinetics of dabigatran for different renal function groups. The trial was performed by Boehringer Ingelheim Pharmaceuticals, Inc.

and submitted as a part of the Pradaxa<sup>®</sup> new drug application. However, the number of patients was small for each renal function group (6 to 11 patients) and there are no clinical data from large-scale trials on dabigatran in patients with severe renal impairment.

Dabigatran has been used in a haemodialysis patient for dialysis anticoagulation because heparin was contraindicated. The dose of 75 mg twice per week was ineffective with clotting of the dialysis membrane. The patient then received a unique dose of 150 mg but developed thrombosis of the arteriovenous fistula. Even if dosing regimen was probably inadequate, dabigatran should be avoided in the haemodialysis setting [42].

Rivaroxaban has a dual mode of elimination. Two thirds of the dose is metabolised in the liver via cytochrome P450 enzymes (CYP3A4, CYP2J2 and CYP-independent mechanisms), half of which is excreted in the urine and half via the faecal route. One-third of the dose is eliminated as unchanged drug in the urine. To investigate the pharmacokinetics and pharmacodynamics of rivaroxaban, the effect of a single oral dose of 10 mg was studied across different renal function groups [43]. The AUC-time curve increased by 44% in subjects with mild renal impairment (CrCl of 50 to 79 ml/min), 52% in those with moderate renal impairment (CrCl of 30 to 49 ml/min), and by 64% in those with severe impairment (CrCl of <30 ml/min), compared with healthy controls. Increased plasma concentrations were also associated with more potent pharmacodynamic effects (inhibition of factor Xa activity and prolongation of prothrombin time).

The ROCKET-AF trial also included subjects with moderate renal insufficiency (CrCl of 30 to 49 ml/min). These patients received 15 mg of rivaroxaban daily based on pharmacokinetic modelling projecting that a 25% dose reduction would lead to similar exposure in patients with moderate renal impairment. In this subgroup of patients, rates of stroke and systemic embolism were higher, regardless of treatment received. The primary event rate (intention to treat analysis) was 2.95 per 100 patient-years with rivaroxaban 15 mg/day compared with 3.44 per 100 patient-years with warfarin (HR 0.86; 95 % CI 0.63 to 1.17). Therefore, the efficacy benefit of rivaroxaban was no longer observed in the subgroup of patients with moderate renal failure. Major bleeding occurred more frequently in patients with renal impairment. However, there was no excess bleeding on rivaroxaban compared with warfarin (HR 0.95; 95% CI 0.72 to 1.26) [44]. Rivaroxaban has not been studied in patients with severe renal impairment (CrCl <30 ml/min).

Apixaban is eliminated via oxidative metabolism, renal, and intestinal routes. After oral administration, urinary excretion represents a significant elimination pathway (approximately 22% of the recovered dose) [1]. In the ARISTOTLE trial, the 2.5 mg twice-daily dose was used in patients with serum creatinine level of 133  $\mu\text{mol/l}$  or more instead of the standard 5 mg bid dose. Patients with serum creatinine levels of 220  $\mu\text{mol/l}$  or more, or with calculated creatinine clearance of <25 ml/min were not included in the study [11]. The primary event rate (stroke or systemic embolism) was similar with apixaban (2.1 per 100 patient-years) and warfarin (2.7 per 100 patient-years)

in the subgroup of patients with moderate or severe renal impairment. Therefore, the significant efficacy advantage of apixaban demonstrated in the study was not present in this subgroup. Patients with moderate or severe renal impairment exhibited a significant increase in major bleeding events compared with the patients with normal renal function (from 1.5 to 3.2 per 100 patient-years for apixaban-treated patients and from 1.8 to 6.4 per 100 patient-years for warfarin-treated patients). The safety benefit of apixaban in comparison to warfarin was persistent in the moderate-severe renal impairment subgroup [11]. In the AMPLIFY trial, the overall rates (regardless of the treatment group) of recurrent VTE or VTE-related death and major bleeding events were higher in patients with moderate or severe renal impairment (4.3% and 4.1%, respectively) compared with patients with normal renal function (2.4% and 0.9%, respectively). The safety benefit of apixaban was no longer present in patients with mild or moderate-severe renal impairment [7].

Edoxaban is the newest of the direct factor Xa inhibitors. Its oral bioavailability is 62%, and 50% is excreted by the kidney [12]. In the HOKUSAI-VTE trial, the 30 mg once daily dose was used in patients with estimated creatinine clearance of 30–50 ml/min. For the primary efficacy endpoint of VTE recurrence or VTE-related death, a trend favouring edoxaban was present in patients with moderate kidney impairment (3% event rate in edoxaban-treated patients versus 5.9% for standard treatment), but no statistically significant interaction was identified between creatinine clearance and treatment group. The safety benefit of edoxaban regarding major or clinically relevant bleeding events was no longer present in patients with creatinine clearance of 30 to 50 ml/min [8].

It must be emphasised that the method used for renal function estimation may significantly influence the administered doses, especially in elderly patients. In a retrospective study, use of the Cockcroft-Gault equation instead of the abbreviated MDRD equation 4 resulted in significantly lower estimated renal function value in patients >65 years old. Data simulation showed that MDRD would result in a 25% higher mean dose of dabigatran [45].

Available evidence for efficacy and security outcomes with DOACs in patients with kidney impairment is summarised in table 4. Table 5 shows the proposed dose adjustments in chronic kidney disease for the DOACs. It must be noted that the proposed dosing regimens are mainly derived from studies for stroke prevention in AF.

### Liver disease

Liver toxicity of the DOACs has become a concern since the first oral thrombin inhibitor, ximelagatran, was withdrawn from market because of safety concerns that were apparent only after prolonged administration (more than 35 days) [46]. Theoretically, the renal clearance of dabigatran could be an advantage.

The major large-scale phase III clinical trials investigating dabigatran and rivaroxaban did not include patients with clinically significant liver disease (acute or chronic hepatitis, cirrhosis or asymptomatic elevation on aminotransferase levels exceeding three times the upper limit of the normal

range). Liver function was carefully monitored without any suggestion of toxicity throughout the studies [4–5, 9].

A phase I trial studied the effect of a single dose of apixaban 5 mg in 16 patients with mild or moderate hepatic impairment (Child-Pugh A or B cirrhosis). The drug had a predictable pharmacokinetic and pharmacodynamic profile and authors implied that dose adjustment is not necessary in these patients [47]. However, a strongly enhanced anticoagulant response, as measured by the PT or the aPTT, was observed when dabigatran or rivaroxaban were added to plasma from patients with liver disease [48].

A recent study evaluated postmarketing cases of liver injury associated with rivaroxaban [49]. Three cases met the biochemical criteria of Hy's law (ALT >3x ULN and total bilirubin >2x ULN). However, these patients were also receiving paracetamol. At least one of these cases could be attributed to rivaroxaban with a high probability.

At least 10% of patients fulfilling Hy's law criteria may develop severe or even fatal hepatic toxicity. The FDA states that finding one Hy's law case in the pre-marketing setting is worrisome; two is considered highly predictive that the drug has the potential to cause severe drug-induced liver injury when given to a larger population. Therefore, pharmacoepidemiological studies are necessary in order to reliably estimate absolute and relative risks of liver injury with rivaroxaban. In the meanwhile, symptoms or signs of liver disease in patients on rivaroxaban should be considered as a potential adverse drug effect. In the absence of any other likely cause, rivaroxaban should be stopped as soon as possible.

In conclusion, there is limited clinical experience in patients with liver disease and these drugs should be withheld awaiting more evidence in this setting.

### Patients with mechanical heart valves

Dabigatran should not be used in patients with mechanical heart valves. The RE-ALIGN trial was prematurely interrupted due to an excess of thromboembolic and bleeding events in the dabigatran users in comparison to warfarin [50]. Warfarin inhibits the activation of both tissue factor-induced pathway and contact pathway-induced coagulation, whereas dabigatran exclusively inhibits thrombin. In cases of intense contact activation, as may happen during exposure of blood to the valve leaflets and the sewing ring, the resulting thrombin generation may exceed local levels of dabigatran, leading to increased thromboembolic complications [50]. The choice of target trough plasma levels may also be an issue, but use of higher dabigatran dose would probably be associated with unacceptably elevated bleeding rates.

### Patients with cancer

Potential indications of the DOACs are currently being studied. No study specifically investigated these drugs in the management of cancer-associated VTE [51]. A small percentage of randomised patients in the aforementioned large phase III clinical trials had cancer. A subgroup analysis of the cancer patients in the RE-COVER study demonstrated a similar frequency of VTE recurrences with dabigatran versus warfarin [6]. The EINSTEIN trials suggest that rivaroxaban may be as effective and safe as stand-

ard treatment for cancer patients with VTE. In the AMPLIFY or HOKUSAI-VTE trials, no subgroup analyses were conducted among patients with cancer. However, the number of patients studied is small and the *post hoc* nature of analyses does not permit any definite conclusion [51]. Dabigatran has been reported to be effective for the treatment of recurrent paraneoplastic VTE in combination with fondaparinux [52].

### Heparin-induced thrombocytopenia

Rivaroxaban does not cross-react in the presence of heparin-induced thrombocytopenia (HIT) antibodies *in vitro* and may be a suitable anticoagulant for the management of patients with HIT [53].

### Monitoring and reversal

A common feature shared by the new anticoagulants is that they have a predictable anticoagulant response and a large therapeutic window allowing fixed dosing with no need for routine monitoring [54]. However, quantification of the drug may still be valuable in certain circumstances such as patients with decreased renal function during acute diseases, for compliance issues or before surgery [55].

The classical coagulation assays usually used for conventional anticoagulants such as the prothrombin time (INR)

for VKA and aPTT for unfractionated heparin do not precisely assess the anticoagulant effect of these new oral agents and their sensitivity depends on the reagent used. However, anti-Xa assay with appropriate calibrators and a modified thrombin time (Hemoclot<sup>®</sup> thrombin inhibitor, Hyphen Biomed) are considered as reliable assays to evaluate the anticoagulant effect of rivaroxaban and dabigatran, respectively [56]. It must be emphasised that, due to the relatively short half-life of the DOACs, the timing of the last dose is of utmost importance to evaluate the coagulation tests results.

Although data on safety issues originating from the pivotal studies as well as post-marketing evaluation are reassuring [57], serious bleeding events may still occur and their management remains a challenge. Indeed, there is no specific antidote to these new drugs. Several nonspecific agents have been studied, mostly in animal models or in healthy subjects with biological endpoints and yielded contrasting results. Altogether, it seems that prothrombin complex concentrates (PCC) should be used for rivaroxaban while activated PCC should be preferred for dabigatran [58]. Recombinant activated factor VII yielded rather disappointing results and should be used as a second line treatment. A specific antidote for dabigatran is being developed and seems to effectively reverse its anticoagulant effect in human plasma *in vitro* [59].

**Table 4:** Efficacy and safety of direct oral anticoagulants in patients with moderate renal impairment versus normal renal function. Direct comparison of outcomes between different drugs is discouraged, as definition of moderate renal impairment is not uniform throughout the different studies.

Studied drug	Outcome	No renal impairment: CrCl >80 ml/min for apixaban-dabigatran, >49 ml/min for rivaroxaban			Moderate renal impairment: CrCl <50 ml/min for apixaban-dabigatran, 30–49 ml/min for rivaroxaban		
		DOAC	Standard treatment	HR	DOAC	Standard treatment	HR
Apixaban [11] (2.5 mg bid in the case of renal impairment)	Stroke -systemic embolism per 100 patient-years	1.0	1.1	N.S.	2.1	2.7	NS
	Major bleeding events per 100 patient-years	1.5	1.8	N.S.	3.2	6.4	Favours apixaban
Apixaban [7]	Recurrent VTE / VTE-related death at 6 months	2.3	2.4	N.S.	4.1	4.4	NS
	Major bleeding events at 6 months	0.3	1.4	Favours apixaban	2.9	5.5	NS
Dabigatran 150 mg bid [21] (110 mg bid in the case of renal impairment)	Major bleeding events per 100 patient-years	2.09	2.36	N.S.	5.29	5.41	NS
Rivaroxaban 20 mg qd [47] (15 mg qd in the case of renal impairment)	Stroke -systemic embolism per 100 patient-years (ITT analysis)	1.92	2.16	0.89 (0.73–1.08)	2.95	3.44	0.86 (0.63–1.17)
	Major bleeding events per 100 patient-years	3.39	3.17	1.07 (0.91–1.26)	4.49	4.70	0.95 (0.72–1.26)
Edoxaban 60 mg qd [8] (30 mg qd in the case of renal impairment)	Recurrent VTE / VTE-related death at 3–12 months	3.2	3.4	N.S.	3.0	5.9	NS

bid = twice daily; qd, once daily; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; HR = hazard ratio; ITT = intention to treat; NS = not statistically significant difference; VKA = vitamin K antagonists

**Table 5:** Dosing recommendations for direct oral anticoagulants in patients with chronic kidney disease. Dosing regimens are mostly derived from studies for stroke prevention in atrial fibrillation (see text).

Drug	Chronic kidney disease stage		
	III (GFR 30–50 ml/min)	IV (GFR 15–30 ml/min)	V (GFR <15 ml/min)
Rivaroxaban	15 mg qd	Contraindicated	
Dabigatran	110 mg bid	75 mg bid (to be avoided) <sup>a</sup>	Contraindicated
Apixaban <sup>b</sup>	2.5 mg bid	Contraindicated	
Edoxaban	30 mg qd	Contraindicated	

Bid = twice daily GFR = glomerular filtration rate; qd = once daily

<sup>a</sup> Pharmacokinetic data only, no clinical data.

<sup>b</sup> For apixaban, stage III chronic kidney disease was defined as creatinine level >133 µmol/l; stage IV–V, as creatinine level >220 µmol/l or creatinine clearance of <25 ml/min

## Conclusion

Direct oral anticoagulants are an attractive option for patients requiring long-term anticoagulation treatment. They have a rapid onset of action and can be administered at fixed doses without the need for routine anticoagulation monitoring. They may present fewer interactions than warfarin but further studies are needed to assess the clinical significance of the interactions with CYP3A and P-gp inhibitors/inducers. A higher rate of bleeding has been observed in association with antiplatelet agents or NSAIDs. Their safety profile has not been sufficiently studied in the elderly, and in patients with liver disease or severe renal impairment. Dose adjustment is necessary in patients with moderate renal impairment and a higher bleeding rate has been observed in this subgroup, although not higher than with warfarin. The clinical settings that require monitoring of coagulation assays have not yet been well specified. Reversal of their anticoagulant effect may be problematic in case of severe bleeding. Therefore, despite the obvious advantages of the DOACs, experience is still lacking for many patient subgroups in which they should be withheld awaiting more data.

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