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EDITOR'S PICK

Direct oral anticoagulants (DOAC) provide clinicians with a valuable method for the prevention and treatment of thrombotic events. However, DOAC also expose patients to the risk of bleeding or major bleeding, which can lead to major adverse events as a result of their inappropriate use. This article by Vornicu et al. highlights the various aspects that require consideration in order to minimise the incidence of these adverse events and points to the approaches available to ensure this can be done effectively. The article also provides important practical guidance in specific situations where DOAC are vulnerable to mismanagement.

MINIMISATION OF BLEEDING RISKS DUE TO DIRECT ORAL ANTICOAGULANTS

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ABSTRACT

Direct oral anticoagulants (DOAC) are used in several indications for the prevention and treatment of thrombotic events. As highlighted by data from clinical trials and case studies, all DOAC carry the risk of bleeding despite careful selection and patient management. Previous publications have demonstrated the limited knowledge of many physicians concerning the indications for, and correct management of, these anticoagulants. Health institutions should develop risk minimisation strategies and educational materials to prevent major adverse events related to DOAC administration. Major bleeding events are reported in clinical practice and specific antidotes are emerging from Phase III trials. Some antidotes are licensed but their high cost might limit routine use. We therefore illustrate approaches and tools that can help physicians prescribe DOAC appropriately. We focus on screening for modifiable bleeding risk factors and adapting doses according to the individual benefit-risk profile. We also provide recommendations on managing a missed dose, switching, bridging, and resumption.

Keywords: Prevention, bleeding, direct oral anticoagulants (DOAC).

INTRODUCTION

Bleeding events have been reported in all the major clinical trials comparing direct oral anticoagulants (DOAC) with other anticoagulants despite regular monitoring of adverse events, strong medication adherence, and careful patient selection.[1-4]

Large randomised trials comparing bleeding risks of different DOAC are not available as DOAC have always been compared with warfarin, low molecular weight heparin (LMWH), and antiplatelet agents. When DOAC were prescribed at prophylactic doses in orthopaedic surgery, rates of bleeding were similar to LMWHs.[5] When DOAC were prescribed for patients with non-valvular atrial fibrillation (NVAF) or venous thromboembolism (VTE), a recent meta-analysis showed a lower rate of fatal bleeding and case-fatality of major bleeding (MB) events for DOAC than with warfarin.[6] Another meta-analysis showed that patients with a creatinine clearance (CrCl) between 50–80 mL/min who received DOAC had significantly fewer MB events than those receiving vitamin K antagonists (VKA). For patients with CrCl <50 mL/min, the difference in MB was not statistically significant, but using indirect comparisons, apixaban was associated with significantly fewer MB episodes than other DOAC.[7]

Post-marketing surveillance registries provide real-world data on the safety and efficacy of DOAC. A retrospective cohort study of Medicare beneficiaries with NVAF found a higher incidence of MB with dabigatran than with warfarin, regardless of anatomical site.[8] A smaller Italian cohort study revealed a safe profile of either 110 mg or 150 mg dabigatran twice daily (bid), regarding fatal bleeding in patients at high risk of haemorrhage and thromboembolism.[9] The Dresden New Oral Anticoagulants (NOAC) registry found that the routine safety profile of dabigatran etexilate (DE) was no worse than that reported in the RE-LY trial even if selection bias might exist.[10] The Danish national registry found a higher bleeding rate in previous VKA users than VKA-naïve patients. This observation may reflect patient selection and 'drug switching' practices.[11] Concerning rivaroxaban, a large observational study showed that the MB rate was generally consistent with registration trial results and that fatal bleeds were rare.[12] The MB rate with rivaroxaban from the Dresden NOAC registry was lower than that for VKA.[13] However, the ROCKET AF trial identified age, sex, diastolic blood pressure, prior gastrointestinal bleeding, prior aspirin use, and anaemia as clinically relevant factors associated with MB risk with rivaroxaban and VKA.[14] This review aims to discuss strategies to prevent DOAC-related bleeding in normal clinical practice.

HOW TO PREVENT MAJOR BLEEDING

Various aspects of the management of patients treated with DOAC should be highlighted to reduce the incidence of MB.

Appropriate Use of Direct Oral Anticoagulants

Off-label use or misuse

The off-label use or misuse of DOAC means use outside of approved indication, at an inappropriate dose, or an inappropriate choice of DOAC according to patient characteristics. Inappropriate use is frequent (occurring in 8–49% of patients) and may cause infra or supra-therapeutic anticoagulation carrying risks of thromboembolism or severe, even fatal bleeding (Table 1).[11,15-19] A recent publication indicated a significant risk for patients related to lack of physicians' knowledge about DOAC and highlighted the need for additional education and training.[20]

Renal function

Renal failure is the most common risk factor associated with bleeding in elderly patients, and should therefore be assessed before initiating DOAC and during treatment.[21] The updated European Heart Rhythm Association (EHRA) practical guide on the use of DOAC suggests that renal function should be checked every 6 months in patients >75–80 years (especially those on DE or edoxaban), and in frail patients.[22] The proposed recheck interval (in months) is the CrCl divided by 10, if the CrCl is <60 mL/min. More frequent checks are recommended in patients with conditions that might affect renal function. In clinical trials of DOAC for NVAF, drug eligibility and dosing were determined using the Cockcroft–Gault equation to estimate CrCl. The modification of diet in renal disease equation (used to estimate glomerular filtration rate) tends, at low estimate glomerular filtration rate values, to overestimate renal function compared with the Cockcroft–Gault equation.[23,24] This overestimation may lead to incorrect decisions about eligibility or dose.

Bioavailability

If DE capsules are opened, the bioavailability increases to 75% and the bleeding risk is greatly enhanced.[25] Therefore, DE should not be given via a gastrostomy or jejunostomy and capsules should not be opened or crushed before administration. Rivaroxaban and apixaban have similar bioavailability when administered in crushed form mixed with apple sauce or water through a nasogastric tube or gastrostomy.[26,27] To the best of our knowledge, there are currently no data available for edoxaban.

Table 1: Summary of pharmacokinetic properties, indication, and dose regimens of direct oral anticoagulants in the European Union.[29,35,46,54,62-83]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
T_{max} (hours)	1.5–3.0	2.0–4.0	3.0–4.0	1.0–2.0
Distribution volume (L)	60–70	±50	23	107
Half-life (hours)	11: healthy individuals 12–13: elderly	5–9: healthy individuals 11–13: elderly	8–15: healthy individuals	10–14
Bioavailability	3–7% pH sensitive	2.5–10 mg dose: 80–100% (fasting/fed) 15–20 mg dose: 66% (fasting) ± 100% (fed)	±50%	62%
Protein binding	35%	>90%	87%	55%
Metabolism	Conjugation	CYP-dependent and independent mechanisms	CYP-dependent mechanisms	CYP-dependent (<5%) and independent mechanisms (<10%)
Active metabolites	Yes: glucuronide conjugates	No	No	Yes (<15%)
Elimination	80% renal	33% unchanged via the kidney	27% renal	50% renal
	20% bile (glucuronide conjugation)	66% metabolised in the liver into inactive metabolites eliminated via the kidney (50%) or the colon (50%)	73% through the liver while the residue is excreted by the hepatobiliary route	50% metabolism and biliary/intestinal excretion
Effects of food	T_{max} delayed; C_{max} & AUC unchanged	T_{max} delayed; C_{max} & AUC increased (15–20 mg)	T_{max} delayed; C_{max} & AUC unchanged	C_{max} increased, but minimal effect on total exposure
CYP substrate	No	CYP3A4, CYP2J2	CYP3A4	CYP3A4 (<5%)
P-gp substrate	DE: Yes	Yes	Yes	Yes
Venous thromboembolism Prophylaxis	**220 mg/day** (2 caps 110 mg qd) C_{max}: 71 (35–162) ng/mL (mean; 25–75 PCTL) C_{min}: 22 (13–36) ng/mL (mean; 25–75 PCTL) **150 mg/day** (2 caps 75 mg qd) → if CrCl 30–50 mL/min, if >75 years, if verapamil, amiodarone, and quinidine THR: 28–35 days TKR: 10 days	**10 mg/day** (1 tablet 10 mg qd) C_{max}: 125 (91–196) ng/mL (median; 5–95 PCTL) C_{min}: 9 (1–38) ng/mL (median; 5–95 PCTL) THR: 5 weeks TKR: 2 weeks	**5 mg/day** (1 tablet 2.5 mg bid) C_{max}: 77 (41–146) ng/mL (median; 5–95 PCTL) C_{min}: 51 (23– 109) ng/mL (median; 5–95 PCTL) THR: 32–38 days TKR: 10 days	× (EU)

Table 1 continued.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Non-valvular atrial fibrillation*	**300 mg/day** (1 caps 150 mg bid) C_{max}: 175 (117-275) ng/mL (mean; 25–75 PCTL) C_{min}: 91 (61-143-200) ng/mL (mean; 25–75–90 PCTL) **220 mg/day** (1 caps 110 mg bid) → if >80 years or verapamil	**20 mg/day** (1 tablet 20 mg qd) C_{max}: 249 (184–343) ng/mL (mean; 5–95 PCTL) C_{min}: 44 (12–137) ng/mL (mean; 5–95 PCTL) **15 mg/day** (1 tablet 15 mg qd) → if CrCl between 15-49 mL/min C_{max}: 229 (178–313) ng/mL (mean: 5–95 PCTL) C_{min}: 57 (18–136) ng/mL (mean; 5–95 PCTL)	**10 mg/day** (1 tablet 5 mg bid) C_{max}: 171 (91–321) ng/mL (median; 5–95 PCTL) C_{min}: 103 (41–230) ng/mL (median; 5–95 PCTL) **5 mg/day** (1 tablet 2.5 mg bid) → If at least 2 of the following conditions: ≥80 years, ≤60 kg or serum creatinine ≥ 1.5 mg/dL; → Or if CrCl 15-29 mL/min C_{max}: 123 (69–221) ng/mL (median; 5–95 PCTL) C_{min}: 79 (34–162) ng/mL (median; 5–95 PCTL)	**60 mg/day** (1 tablet 60 mg qd) C_{max}: +/-170 (165–195) ng/mL (median; IQR) C_{min}: 36 (19–62) ng/mL (median; IQR) **30 mg/day** (1 tablet 30 mg qd) → if CrCl between 15–50 mL/min, ≤60 kg or concomitant use of dronedarone, erythromycin, ketoconazole, ciclosporin C_{min}: 27 (15–45) ng/mL (median; IQR)
Venous thromboembolism treatment	**300 mg/day** (1 caps 150 mg bid) after at least 5 days of parenteral anticoagulants C_{max}: 175 (117–275) ng/mL (mean; 25–75 PCTL) C_{min}: 60 (39–95–146) ng/mL (mean; 25–75–90 PCTL) **220 mg/day** (1 caps 110 mg bid) → if >80 years or verapamil	**Treatment phase:** **30 mg/day** (1 tablet 15 mg bid) for 21 days → followed by **20 mg/day** (1 tablet 20 mg qd) for 3–6 months C_{max}: 270 (189–419) ng/mL (mean; 5–95 PCTL) C_{min}: 26 (6–87) ng/mL (mean; 5–95 PCTL) **15 mg/day** (1 tablet 15 mg qd) → if CrCl between 15–49 mL/min and the risk of bleeding outweighs the risk of recurrent DVT or PE	**Treatment phase:** **20 mg/day** (2 tablet 5 mg bid) for 7 days C_{max}: 251 (111–572) ng/mL (median; 5–95 PCTL) C_{min}: 120 (41–335) ng/mL (median; 5–95 PCTL) → followed by **10 mg/day** (1 tablet 5 mg bid) for 3–6 months C_{max}: 132 (59–302) ng/mL (median; 5–95 PCTL) C_{min}: 63 (22–177) ng/mL (median; 5–95 PCTL) If high risk of recurrent DVT or PE: **5 mg/day** (1 tablet 2.5 mg bid) after 6 months treatment	**60 mg/day** (1 tablet 60 mg qd) after at least 5 days of parenteral anticoagulant treatment **30 mg/day** (1 tablet 30 mg qd) → if CrCl between 15–50 mL/min, BW ≤60 kg or concomitant use of dronedarone, erythromycin, ketoconazole, ciclosporin
Prevention of athero-thrombotic events after ACS with elevated cardiac biomarkers	×	**5 mg/day** (1 tablet 2.5 mg bid) with ASA (75–100 mg) or, ASA + clopidogrel (75 mg) or ticlopidine C_{max}: 46 (28–70) ng/mL (median; 5–95 PCTL) C_{min}: 17 (6–37) ng/mL (median; 5–95 PCTL)	×	×

T_{max}: time to reach peak concentration; C_{max}: peak concentration; AUC: area under the curve; CYP3A4: cytochrome P450 isozyme 3A4; P-gp: P-glycoprotein; BRCP: breast cancer resistance protein; caps: capsule; qd: once daily; bid: twice daily; CrCl: creatinine clearance; DVT: deep-vein thrombosis;

Table 1 continued.

PE: pulmonary embolism; THR: total hip replacement; TKR: total knee replacement; ASA: acetylsalicylic acid; ACS: acute coronary syndrome; C_{max} and C_{min}: peak and trough concentrations providing from the clinical trials; PCTL: percentiles; IQR: interquartile range; BW: body weight; DE: dabigatran etexilate. × = off-label; EU: European Union.

Patient body weight

There is evidence that anticoagulant clearance rates increase with body weight, however optimal dosing strategies for DOAC in obese patients remain unknown.[28] In the RE-LY study, dabigatran concentrations tended to increase with decreasing body weight.[28] Close clinical surveillance is recommended by several authorities because of limited clinical experience in these populations.[29,30]

Kubitza et al.[31] showed that rivaroxaban peak concentration (C_{max}) was increased by 24% in subjects weighing ≤50 kg while the area under the curve (AUC) was unaffected (difference was <25%) by body weight resulting in a small (15%) increase in prolongation of prothrombin time, which was not considered to be clinically relevant. Similarly to dabigatran, no dose adjustment is currently proposed by the European or American agencies.[32]

Regarding apixaban, a 30% and 20% increase in C_{max} and AUC, respectively, have been reported in patients weighing <50 kg.[33] Since body weight seems to have a modest effect on apixaban exposure, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend dose adjustment in patients weighing <60 kg (2.5 mg bid instead of 5 mg bid) in the presence of additional risk factors, namely age ≥80 years or serum creatinine >1.5 mg/dL.[34,35]

Dose adjustment in patients weighing <60 kg is also recommended for edoxaban (30 mg once daily since C_{max} and AUC in patients with low body weight (median 55 kg) were increased by 40% and 13%, respectively, compared with patients with high body weight (median 84 kg) in a population pharmacokinetic analysis of the ENGAGE AF-TIMI 48 study in NVAF.[36]

Patients with impaired hepatic function

The manufacturer's recommendations for DOAC in patients with impaired hepatic function are based on both Child–Pugh classification and liver-related exclusion criteria applied in clinical trials (elevated liver enzymes [aspartate transaminase/alanine transaminase] >2-times the upper limit of normal or total bilirubin ≥1.5-times the upper limit of normal).[37] The EMA contraindicates the use of dabigatran in patients with hepatic impairment or liver disease expected to have any impact on survival.[29]

In contrast to dabigatran, liver metabolism is an important route of elimination for FXa inhibitors. Approximately two-thirds of the administered rivaroxaban dose is metabolised by the liver via CYP3A4, 2J2, and CYP-independent mechanisms into inactive metabolites.[32] Apixaban undergoes liver metabolism mainly via CYP3A4/5, but other isoenzymes are also involved, while edoxaban is metabolised via carboxylesterase-1 hydrolysis, conjugation, or oxidation by CYP3A4/5 (<10%). Therefore, the EMA contraindicates their use in cases of hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Apixaban and edoxaban are not recommended in patients with severe hepatic impairment, rivaroxaban is also contraindicated in cirrhotic patients with Child–Pugh B/C. Although one limited study showed a similar bleeding risk in Child–Pugh A/B cirrhosis patients treated with apixaban or rivaroxaban compared with traditional anticoagulants, further evaluations and larger studies are needed to better inform clinicians' decision-making.[38]

Drug interactions

In addition to these specific populations, DOAC also interact with P-glycoprotein substrates and CYP3A4 inhibitors, which may greatly increase their plasma concentrations, and hence, bleeding risks. Table 2 summarises drug-drug interactions reported in the literature as well as recommendations for dose adaptation and contraindications for the EMA and FDA prescribing guidelines.[22,39,40] As there is an increased risk of bleeding, DOAC should be used with caution if a concomitant use of antiplatelet agents is indicated[29,32,35] and non-steroidal anti-inflammatory drugs (NSAID) should be avoided if possible.[28,31,39] Concomitant use with

any other anticoagulant is strictly contraindicated, except during switching procedures from DOAC to VKA or when unfractionated heparin (UFH) is given at doses necessary to maintain an open central venous or arterial catheter.[29]

Screening for Bleeding Risk Factors

Non-modifiable and potentially reversible clinical features associated with higher bleeding risks must be carefully identified when initiating DOAC therapy and assessed regularly throughout treatment. Various risk stratification scores can help clinical decision-making.[41,42] The bleeding risk score HAS-BLED has shown better performance than the HEMORR(2)HAGES and ATRIA risk scores in predicting MB in anticoagulated AF patients.[41] A value ≥3 indicates a high risk for haemorrhage and suggests review and correction of modifiable risk factors (hypertension, renal/hepatic impairment, alcohol excess, concomitant use of non-steroidal anti-inflammatory drugs, antiplatelet agents, or selective serotonin reuptake inhibitors). The simple five-element ORBIT AF bleeding risk score (older age [>75 years], reduced haemoglobin/haematocrit history of anaemia, bleeding history, insufficient kidney function, and treatment with antiplatelet agents) had the best ability to predict MB in patients with NVAF compared with HAS-BLED and ATRIA risk scores.[43]

Table 2: Summary of drug-drug interactions with available recommendations for dose adaptation or contraindications by the competent authorities.[22,39,40,83]

		Dabigatran P-gp substrate	Rivaroxaban P-gp and CYP3A4/2J2 substrate	Apixaban P-gp and CYP3A4/5 substrate	Edoxaban P-gp substrate
Molecule	**Mechanism**				
Antiarrhythmics					
Dronedarone	P-gp and CYP3A4 inhibitor	AUC: +114% (400 mg: single dose)*	Minor effect (use with caution if CrCl 15-50 mL/min)†	No data yet	C_{max}: +46% AUC: +85%***
		AUC: +136% (400 mg: multiple doses)			
Quinidine	P-gp competition	AUC: +53% (1,000 mg: single dose)**	Minor effect (use with caution if CrCl 15–50 mL/min)	No data yet	AUC: +77% C_{max}: +85% (300 mg: multiple doses)
Verapamil	P-gp competition and weak CYP3A4 inhibitor	AUC: +18% (120 mg IR: single dose taken 2 hours after DE intake)**/***	Minor effect (use with caution if CrCl 15–50 mL/min)	No data yet	AUC and C_{max}: +53% (240 mg: multiple doses)
		AUC: +143% (120 mg IR: single dose, 1 hour before DE intake)**/***			
		C_{max}: +12% (120 mg IR: single dose taken 2 hours after DE intake)**/***			
		C_{max}: +179% (120 mg IR: single dose, 1 hour before DE intake)**/***			
Amiodarone	P-gp competition	AUC: +58% (600 mg: single dose)**	Minor effect (use with caution if CrCl 15–50 mL/min)	No clinically relevant effect	AUC: +40% C_{max}: +66% (400 mg: single dose)

Table 2 continued.

		Dabigatran P-gp substrate	Rivaroxaban P-gp and CYP3A4/2J2 substrate	Apixaban P-gp and CYP3A4/5 substrate	Edoxaban P-gp substrate
Molecule	**Mechanism**				
Diltiazem	P-gp and CYP3A4 inhibitor	No effect	Minor effect (use with caution if CrCl 15–50 mL/min)	AUC: +40%	No data yet
Antianginal/antihypertensive drugs					
Ranolazine	P-gp and CYP3A4 inhibitor	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)	No data yet	No data yet
Felodipine	P-gp and CYP3A4 inhibitor	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)	No data yet	No data yet
Anti-inflammatory					
Naproxen	P-gp competition	No data yet	AUC: +10% (500 mg)	C_{max}: +61% AUC: +55% (500 mg)	No effect, but pharmacod namically increased bleeding time
Antihypercholesterolemiant					
Atorvastatin	P-gp and CYP3A4 substrate	AUC: +18%	No effect	No PK data yet	No effect
Antimycotic					
Ketoconazole	P-gp and CYP3A4 inhibitor	AUC: +138% (400 mg: single dose)*	C_{max}: +72% (400 mg: single dose †	C_{max}: +62% (400 mg multiple doses)†	C_{max}: +89%*** (400 mg multiple doses)
		AUC: +153% (400 mg: multiple doses)	AUC: +158% (400 mg: single dose)†	AUC: +100% (400 mg multiple doses)†	AUC: +87% *** (400 mg multiple doses)
Itraconazole	P-gp and CYP3A4 inhibitor	No data yet*	No data yet, but similar results than ketoconazole are expected†	No data yet, but similar results than ketoconazole are expected†	No data yet
Voriconazole	P-gp and CYP3A4 inhibitor	No data yet			No data yet
Posaconazole	P-gp and CYP3A4 inhibitor	No data yet***	No data yet†		No data yet
Fluconazole	CYP3A4 inhibitor	No data yet - supposed no effect	C_{max}: +28% AUC: +42%	No data yet	No data yet
Antibacterial					
Clarithromycin	P-gp and CYP3A4 inhibitor	C_{max}: +49%		No data yet	No data yet
		AUC: +60%	AUC: +54% (500 mg multiple doses)		
Azithromycin	P-gp and CYP3A4 inhibitor	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)	No data yet	No data yet
Erythromycin	P-gp and CYP3A4 inhibitor	No data yet	AUC: +34% (500 mg multiple doses)	No data yet	C_{max}: +68%*** AUC: +85%***
Rifampicin	P-gp and CYP3A4 inducer	C_{max}: -65,5%† AUC: -67%† (600 mg: multiple doses)	AUC: -50%†	AUC: -54%†	AUC: -35% but with compensatory increase of active metabolite (avoid if possible)

Table 2 continued.

		Dabigatran P-gp substrate	Rivaroxaban P-gp and CYP3A4/2J2 substrate	Apixaban P-gp and CYP3A4/5 substrate	Edoxaban P-gp substrate
Molecule	**Mechanism**				
Protease inhibitors					
Ritonavir	P-gp and CYP 3A4 inhibitor	No data yet†	C_{max}: +55% (600 mg multiple doses)†	No PK data but strong increase†	No data yet†
			AUC: +153% (600 mg multiple doses)†		
Immunosuppressor					
Ciclosporine	P-gp competition	No data yet*	AUC: +50%	No data yet	AUC: +73%*** C_{max}: +74% (500 mg single dose)
Tacrolimus	P-gp competition	No data yet†	AUC: +50%	No data yet	No data yet

*Contraindicated by the European Medicines Agency (EMA).
**The EMA recommends dose reduction for dabigatran: from 220 mg qd to 150 mg qd in prevention of VTE in joint replacement.
***The EMA recommends dose reduction for dabigatran: from 150 mg bid to 110 mg bid) in patients with NVAF or VTE; and for edoxaban a dose reduction of 50% (30 mg qd) in patients with NVAF or VTE.
†Concomitant treatment with these drugs are not recommended by the EMA.
NVAF: non-valvular arterial fibrillation; VTE: venous thromboembolism; P-gp: p-glycoprotein; CYP: cytochrome; AUC: area under the curve; CrCl: creatinine clearance; PK: pharmacokinetics; C_{max}/C_{min}: peak and trough concentrations providing from the clinical trials; qd: once daily; bid: twice daily; DE: dabigatran etexilate.

Screening for injuries (e.g. recent intracranial haemorrhage) and conditions (e.g. colon cancer) that may lead to MB is essential before starting DOAC therapy.

Particular attention should be paid to renal protective strategies for patients on dabigatran and edoxaban. These patients should be informed about the impact of concurrent medications (e.g. NSAID) or comorbidities (e.g. dehydration) on their renal function, which could lead to an enhanced and prolonged anticoagulant effect.

Adapting Direct Oral Anticoagulant Dosage to Individual Benefit-Risk Ratios

Why and when?

Several criteria should be taken into account when considering drug monitoring: 1) intra and 2) inter-individual variability in plasma drug level, both justifying the identification of the optimal dose for the individual at the start of treatment, 3) variability and reproducibility of the testing method, 4) correlation between drug level and clinical outcome, and 5) the therapeutic value of drug monitoring.

DOAC demonstrate high intra and inter-individual variability depending on patients' age, renal and hepatic function, drug-drug interactions, and body weight.[44] While package inserts recommend dose adaptation according to the patient's characteristics, they do not give guidance for patients with multiple interfering factors in whom a targeted plasma level cannot be reached. The importance of targeted plasma levels is supported by analysis of large trials (RE-LY and the ENGAGE-AF TIMI 48), which showed that plasma concentrations of dabigatran and edoxaban were correlated with the incidence of MB and thrombotic events.[45-47] Although there are currently no published data for rivaroxaban and apixaban, data from the FDA Clinical Pharmacology and Biopharmaceutics Reviews (available at

http://www.fda.gov) clearly suggest an association between drug exposure and safety outcomes. Thus, patients may benefit from individualised dose tailoring.

In addition, specific situations require an assessment of the intensity of anticoagulation to prevent bleeding and other complications. These include the peri-procedural management of urgent surgery or elective procedures, before thrombolysis or percutaneous coronary intervention, and bridging therapy. Patients on dual antiplatelet therapy added to DOAC could also benefit from a reduced posology to prevent bleeding.[48]

How to handle and perform such measurements?

Compared to VKA, the effect of DOAC on clotting tests varies greatly depending on the time between the last dose and blood sampling (Table 1).[49] Therefore, the time of the last dose in relation to the blood sampling must be known in order to interpret the results of a particular test.

In ambulatory patients, regulatory documents only state thresholds associated with a risk of bleeding for dabigatran. The cut-offs proposed for apixaban, rivaroxaban, and edoxaban are based on the pharmacokinetic characteristics of these drugs where it is suggested that exceeding the highest percentile of a trough concentration carries a risk of bleeding. Regarding which test should be used, Table 3 summarises recommendations depending on the situation and the drug. While limitations have been mentioned for routine coagulation tests such as prothrombin time, activated partial thromboplastin time, and even thrombin time,[50,51] the aim of this comprehensive approach is to provide reliable options, even for laboratories where more specific tests are not available, to give physicians sufficient information to support their clinical decisions.

Dealing with Missed Doses

If a missed dose is noticed within 6 hours of the correct time for dabigatran/apixaban or within 12 hours for edoxaban/rivaroxaban, patients should take the forgotten dose immediately. Beyond these times, the dose should be skipped and the next scheduled dose should be taken.[22]

Table 3: Current indication, clinical need, and required assay characteristics for the measurement of direct oral anticoagulants.[49-51]

Indication	Emergent situation†	Information required	Characteristic of the assay	Assays recommended††
Bleeding	Yes	Identifying above on-therapy levels	• Sensitive (qualitative and quantitative) • Rapid turn-around time	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors) • Global coagulation tests (i.e. PT (rivaroxaban - edoxaban) - aPTT (dabigatran) or dRVVT)
Elective invasive procedure	No	Excluding on-therapy level and ensure safe procedure‡	• Sensitive (qualitative and quantitative) • Accurate	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors) • Thrombin time (dabigatran)
Urgent invasive procedure	Yes	Excluding on-therapy levels and ensure safe procedure‡	• Sensitive (qualitative and quantitative) • Accurate • Rapid turn-around time	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors) • Global coagulation tests (i.e. PT (rivaroxaban edoxaban) - aPTT (dabigatran) or dRVVT) • Thrombin time (dabigatran)
Thrombolysis	Yes	Exclude on-therapy drug level and ensure safe procedure	• Sensitive (qualitative and quantitative) • Accurate • Rapid turn-around time	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors) • Thrombin time (dabigatran)

Table 3 continued.

Indication	Emergent situation†	Information required	Characteristic of the assay	Assays recommended††
Overdose (without complication)	No	Detection of overdose and inform on period at risk of bleeding	• Sensitive (qualitative and quantitative) • Rapid turn-around time	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors) • Global coagulation tests (i.e. PT (rivaroxaban edoxaban) - aPTT (dabigatran) or dRVVT)
Factors interfering with pharmacokinetics (drug interactions, renal or hepatic impairment, genetic polymorphism)	No	Ensure on-therapy level and exclude too low or too high drug levels	• Accurate quantitative test	• Specific coagulation tests (i.e. dTT, ECA - dabigatran; chromogenic anti-Xa - direct FXa inhibitors)

†Emergency situations are those in which anticoagulant effects should be measured within 30 minutes.
††Assays recommended are presented from the more to the less suitable among those able to respond the clinical need.
‡The assessment will depend on the type of procedure.
aPTT: activated partial thromboplastin time; dRVVT: dilute Russell's Viper Venom Time; dTT: dilute thrombin time; ECA: ecarin chromogenic assays; PT: prothrombin time; FXa: factor Xa.

A double dose should never be taken to make up for a missed dose except during the first 21 days of rivaroxaban administration for VTE treatment, where two 15 mg tablets may be taken simultaneously if a dose is missed to ensure a total daily dose of 30 mg.[32]

Adherence to Switching Procedures

The correct timing of switching procedures is essential to avoid excessive anticoagulation due to additional effects and to reduce thromboembolic risk due to transitory low anticoagulation. This timing has been fixed for each DOAC taking into account the drug profile and trial protocols.[52] The Dresden NOAC registry reported that 25% of patients did not have an international normalised ratio (INR) measurement before switching from VKA to DE or rivaroxaban.[53]

Practically, when VKA are switched to DOAC, VKA should be discontinued and DOAC should be started as soon as the INR is ≤2 for dabigatran and apixaban, ≤2.5 for edoxaban, or ≤3 for rivaroxaban. The EMA recommends that for patients with a deep vein thrombosis, rivaroxaban should be initiated once the INR is ≤2.5.[22]

When DOAC are switched to VKA, DOAC should be administered concomitantly until the INR reaches an appropriate anticoagulation level. As DOAC can have an impact on the INR measurements, this should be taken just before the next scheduled administration of the DOAC and be rechecked 24 hours later. Close monitoring of the INR is recommended within the first month of switching. For edoxaban, the administration of a half dose is recommended when VKA is started.[22] For DE, the starting time of the VKA should be based on CrCl as follows: 3 days if CrCl is >50 mL/min, 2 days if CrCl is 30–50 mL/min, and 1 day if CrCl is 15–30 mL/min.[29,30]

When switching from DOAC to parenteral anticoagulants (LMWH or UFH), these should be started when the next DOAC dose is due. Inversely, DOAC should be started at the same time or up to 2 hours before the next parenteral anticoagulant dose. For intravenous UFH, DOAC should be started at the time of discontinuation of the infusion.[22,29]

The EMA recommends that edoxaban should be started 4 hours after stopping the UFH infusion.[54] The renal function should be assessed before switching from heparin to DOAC.

Adherence to Bridging Procedures

The peri-procedural interruption of DOAC treatment depends on the bleeding risk of the procedure and the patient's thromboembolic risk. Interruption may require bridging therapy

with LMWH or UFH, especially for patients with high thromboembolic risks ($CHADS_2$ score >4, recent stroke, VTE, or transient ischaemic attack within the past 3 months, hypercoagulable state) and in cases of severe renal impairment when interruption is >96 hours.[55] Recent data showed increased peri-procedural MB events in patients bridged with heparins after DOAC were stopped, with no decrease in the incidence of cardiovascular or thrombotic events compared with patients who were not bridged.[56-58] The BRIDGE-trial showed similar results concerning patients on warfarin.[59] The first prospective perioperative study including patients receiving dabigatran showed a safe profile in terms of haemorrhagic and thrombotic events without the use of LMWH bridging.[60] The use of LMWH bridging after antiplatelet therapy cessation in patients with coronary stents who underwent non-cardiac surgery, showed a worse ischaemic outcome at 30 days and a significant risk of bleeding compared with the group who did not stop antiplatelet therapy and had no bridging.[61] Therefore, arguments for bridging therapy should be balanced, as it may be harmful for some patients, and further studies are needed to validate the safety of bridging therapy in specific populations, for example, thrombophilic patients or patients with high $CHADS_2$ score (5–6).

Resuming DOAC after an invasive procedure should only be considered when haemostasis is achieved, usually 6–8 hours after procedures with a standard risk of bleeding or atraumatic spinal/epidural anaesthesia. For procedures with a high risk of bleeding, DOAC at full therapeutic dosage should be deferred until 48–72 hours after the invasive procedure. This interval is justified by the fact that specific antidotes are not available everywhere in case of postoperative bleeding or re-operation.[22] Furthermore, the high cost of these antidotes may severely limit their use in clinical practice. For cases of prolonged fasting, immobilisation, or patients with high thrombotic risk profile, short-term administration of reduced venous thromboprophylactic or an intermediate dose of LMWH can be considered before resuming DOAC.[22] Renal function should be assessed postoperatively when anticoagulants are resumed.

CONCLUSIONS

Despite the considerable advantages that DOAC bring to the field of anticoagulation, their inappropriate use can lead to a higher than expected risk of bleeding. Continuous education of healthcare practitioners and patients about dose adjustment and compliance guidance should be supported in all health institutions. Modifiable bleeding risk factors should be identified before initiation of DOAC and reviewed regularly. Individual benefit-risk may be improved in some clinical settings or in patients at risk of supra or infra-therapeutic plasma levels by altering the dose following coagulation monitoring. Protocols for switching, bridging, and resuming anticoagulants should be standardised and systems should be designed to optimise the management of patients treated with DOAC.

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REFERENCES

1. Sholzberg M et al. Bleeding complications from the direct oral anticoagulants. BMC Hematol. 2015;15:18.

2. Southworth MR et al. Dabigatran and postmarketing reports of bleeding. N Engl J Med. 2013;368(14):1272-4.

3. Harenberg J et al. Interpretation of endpoints in a network meta-analysis of new oral anticoagulants following total hip or total knee replacement surgery. Thromb Haemost. 2012;108(5):903-12.

4. Huisman MV et al. Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II. Am J Med. 2015;128(12):1306-13.e1.

5. Riva N et al. Major Bleeding and Case Fatality Rate with the Direct Oral Anticoagulants in Orthopedic Surgery: A Systematic Review and Meta-Analysis. Semin Thromb Hemost. 2016;42(1):42-54.

6. Chai-Adisaksopha C et al. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost. 2015;13(11): 2012-20.

7. Raccah BH et al. Major Bleeding and Hemorrhagic Stroke with Direct Oral Anticoagulants in Patients with Renal Failure: Systematic Review and Meta-Analysis of Randomized Trials. Chest. 2016: doi: 10.1016/j.chest.2015.12.029. [Epub ahead of print].

8. Hernandez I et al. Risk of bleeding with dabigatran in atrial fibrillation. JAMA

Intern Med. 2015;175(1):18-24.

9. Russo V et al. Efficacy and safety of dabigatran in a "real-life" population at high thromboembolic and hemorrhagic risk: data from MonaldiCare registry. Eur Rev Med Pharmacol Sci. 2015;19(20): 3961-7.

10. Beyer-Westendorf J et al. Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. Thromb Haemost. 2015;113(6):1247-57.

11. Sorensen R et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open. 2013;3(5): doi: 10.1136/bmjopen-2013-002758.

12. Tamayo S et al. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. Clin Cardiol. 2015;38(2):63-8.

13. Beyer-Westendorf J et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124(6):955-62.

14. Goodman SG et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol. 2014;63(9):891-900.

15. Kirley K et al. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes. 2012;5(5):615-21.

16. Lim SL, Maxwell E. An audit of dabigatran etexilate prescribing in Victoria. Med J Aust. 2013;198(6):314-5.

17. Larock AS et al. Appropriateness of prescribing dabigatran etexilate and rivaroxaban in patients with nonvalvular atrial fibrillation: a prospective study. Ann Pharmacother. 2014;48(10):1258-68.

18. Armbruster AL et al. Evaluation of dabigatran for appropriateness of use and bleeding events in a community hospital setting. Am Health Drug Benefits. 2014;7(7):376-84.

19. Tellor KB et al. Evaluation of the appropriateness of dosing, indication and safety of rivaroxaban in a community hospital. J Clin Pharm Ther. 2015;40(4):447-51.

20. Olaiya A et al. An observational study of direct oral anticoagulant awareness indicating inadequate recognition with potential for patient harm. J Thromb Haemost. 2016:doi: 10.1111/jth.13288. [Epub ahead of print].

21. Schulman S. New oral anticoagulant agents - general features and outcomes in subsets of patients. Thromb Haemost. 2014;111(4):575-82.

22. Heidbuchel H 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(10):1467-507.

23. Hellden A et al. Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly. BMJ Open. 2013;3(4):doi: 10.1136/bmjopen-2013-002686.

24. Maccallum PK et al. Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study. BMJ Open. 2013; 3(9):e003343.

25. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500131783.pdf. Last accessed: 18 February 2016.

26. Moore KT et al. Rivaroxaban crushed tablet suspension characteristics and relative bioavailability in healthy adults when administered orally or via nasogastric Tube. Clinical Pharmacology in Drug Development. 2014;3(4):321-32.

27. Song Y et al. Relative Bioavailability of Apixaban Solution or Crushed Tablet Formulations Administered by Mouth or Nasogastric Tube in Healthy Subjects. Clin Ther. 2015;37(8):1703-12.

28. Patel JP et al. Anticoagulating obese patients in the modern era. Br J Haematol. 2011;155(2):137-49.

29. European Medicines Agency. Summary of Product Characteristics: Pradaxa. 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. Last accessed: 18 February 2016.

30. Food and Drug Administration. Pradaxa: Full Prescribing Information. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf. Last accessed: 18 February 2016.

31. Kubitza D et al. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol. 2007;47(2): 218-26.

32. European Medicines Agency. Summary of Product Characteristics: Xarelto. 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. Last accessed: 18 February 2016.

33. Upreti VV et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. British J Clin Pharmacol. 2013;76(6)908-16.

34. U.S. Food and Drug Administration. Eliquis: Highlights of Prescribing Information. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202155s011lbl.pdf. Last accessed: 18 February 2016.

35. Salazar DE et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. Thromb Haemost. 2012; 107(5):925-36.

36. Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. Clin Pharmacokinet. 2013;52(4):243-54.

37. Intagliata NM et al. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. Dig Dis Sci. 2016. [Epub ahead of print].

38. Nutescu E et al. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis. 2011;31(3):326-43.

39. Walenga JM, Adiguzel C. Drug and dietary interactions of the new and emerging oral anticoagulants. Int J Clin Pract. 2010;64(7):956-67.

40. European Medicines Agency. Summary of Product Characteristics: Eliquis. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Last accessed: 18 February 2016.

41. Apostolakis S et al. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol. 2012;60(9):861-7.

42. Roldan V et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. Chest. 2013;143(1):179-84.

43. O'Brien EC et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J. 2015;36(46):3258-64.

44. Douxfils J et al. Dose tailoring of dabigatran etexilate: obvious or excessive? Expert Opin Drug Saf. 2015;14(8):1283-9.

45. Reilly PA et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial

(Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63(4):321-8.

46. Ruff CT et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. 2015;385(9984):2288-95.

47. Weitz JI et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost. 2010;104(3): 633-41.

48. Lip GY et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J. 2014;35(45):3155-79.

49. Douxfils J et al. Measurement of non-VKA oral anticoagulants versus classic ones: the appropriate use of hemostasis assays. Thromb J. 2014;12:24.

50. Lessire S et al. Is Thrombin Time useful for the assessment of dabigatran concentrations? An in vitro and ex vivo study. Thromb Res. 2015;136(3):693-6.

51. Douxfils J et al. Non-VKA Oral Anticoagulants: Accurate Measurement of Plasma Drug Concentrations. Biomed Res Int. 2015:345138.

52. Guimaraes PO et al. Practical and clinical considerations in assessing patients with atrial fibrillation for switching to non-vitamin K antagonist oral anticoagulants in primary care. Int J Gen Med. 2015;8:283-91.

53. Beyer-Westendorf J et al. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care--results from the Dresden NOAC registry. Br J Clin Pharmacol. 2014;78(4):908-17.

54. European Medicines Agency. Summary of Product Characteristics: Lixiana. 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf. Last accessed: 18 February 2016.

55. Mar PL et al. Periprocedural management of anticoagulation in patients taking novel oral anticoagulants: Review of the literature and recommendations for specific populations and procedures. Int J Cardiol. 2016;202:578-85.

56. Beyer-Westendorf J et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014;35(28):1888-96.

57. Steinberg BA et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation. 2015;131(5):488-94.

58. Douketis JD et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thromb Haemost. 2015;113(3):625-32.

59. Douketis JD et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. New Engl J Med. 2015;373(9):823-33.

60. Schulman S et al. Perioperative Management of Dabigatran: A Prospective Cohort Study. Circulation. 2015;132(3): 167-73.

61. Capodanno D et al. Impact of bridging with perioperative low-molecular-weight heparin on cardiac and bleeding outcomes of stented patients undergoing non-cardiac surgery. Thromb Haemost. 2015;114(2):423-31.

62. Bauersachs R et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. New Eng J Med. 2010;363(26):2499-510.

63. Büller HR et al; EINSTEIN–PE Investigators et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. New Engl J Med. 2012;366(14): 1287-97.

64. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med. 2009;361(12):1139-51.

65. Eriksson BI et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. New Engl J Med. 2008; 358(26):2765-75.

66. Eriksson BI et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. Thromb Haemost. 2011;105(4):721-9.

67. Eriksson BI et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5(11): 2178-85.

68. Eriksson BI et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet. 2007; 370(9591):949-56.

69. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 2011;365(11):981-92.

70. Kakkar AK et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632): 31-9.

71. Lassen MR et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. New Engl J Med. 2008;358(26):2776-86.

72. Lassen MR et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. New Engl J Med. 2010; 363(26):2487-98.

73. Lassen MR et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375(9717):807-15.

74. Lassen MR et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. New Engl J Med. 2009; 361(6):594-604.

75. Mega JL et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683):29-38.

76. Mega JL et al. Rivaroxaban in patients with a recent acute coronary syndrome. New Engl J Med. 2012;366(1):9-19.

77. Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med. 2011;365(10):883-91.

78. Turpie AG et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676): 1673-80.

79. Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 2013;369(22):2093-104.

80. Frost C et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol. 2013;76(5):776-86.

81. Mueck W et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014; 53(1):1-16.

82. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost. 2009;15 Suppl 1:9S-16S.

83. Parasrampuria DA, Truitt KE. Pharmacokinetics and Pharmacodynamics of Edoxaban, a Non-Vitamin K Antagonist Oral Anticoagulant that Inhibits Clotting Factor Xa. Clin Pharmacokinet. 2015. [Epub ahead of print].