Oral Anticoagulation in 2017

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Abstract

In this paper we describe the properties and clinical use of new anticoagulants: dabigatran (a direct thrombin inhibitor) and direct anti-Xa agents (rivaroxaban, apixaban, edoxaban). Major studies that have been performed with these agents in comparison with warfarin are reported. Recommendations for use in clinical practice are provided. Information on the disappearance of the anticoagulant effect after stopping drug intake and on the administration of agents that neutralize the effect of the new anticoagulant is provided.

Keywords : warfarin, dabigatran, anti-Xa agents, idarucizumab

The coagulation system is essential for survival. The main physiological function of the coagulation system is hemostasis, the sealing of leaks in the vasculature to prevent excessive blood loss. Tissue factor surrounding the blood vessels activates the 'classical' or 'extrinsic' activation of coagulation. Activation of coagulation triggers a complex and highly regulated cascade system of sequentially activated proteases, culminating in the generation of thrombin (factor IIa), which converts soluble fibrinogen into an insoluble fibrin network, and is a potent activator of blood platelets. Together, activated platelets and fibrin seal damaged blood vessels (Figure 1).

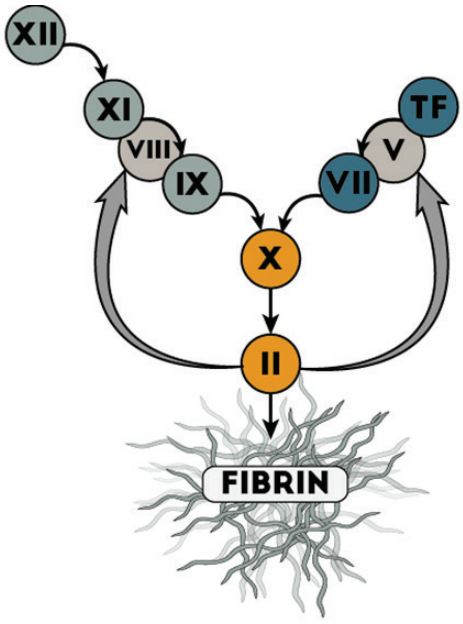


Figure 1: Coagulation can be activated through different pathways. First, through the intrinsic pathway (factor XII and factor XI activation), triggered by contact with foreign bodies or by inflammatory processes, and secondly as a result of tissue factor (TF) release at sites of vessel damage. Activation of factor X to factor Xa is the start of the common pathway, which leads to activation of prothrombin (II) to thrombin (IIa), finally resulting in fibrin generation and clot formation.

On the other hand, excessive or pathological activation of coagulation is the common underlying cause of thrombo-embolic cardiovascular diseases, responsible for one in three deaths. Anticoagulants, drugs that interfere with the coagulation system, are the cornerstone of the prevention and treatment of various clinical manifestations of thrombosis, such as venous thromboembolism (VTE), atrial fibrillation (AF), and thrombosis on mechanical prosthetic heart valves.

The first generation of oral anticoagulants were discovered in the United States in the 1930s as a result of the investigation into the mysterious death of cows due to excessive bleeding. Dr. Karl Link was able to isolate the anticoagulant dicoumarol in moldy clover used as cattle food.[1] Warfarin, the first commercially available coumarin derivative, was first marketed as a rodenticide. It was not until the 1950s that warfarin started to be used in patients, gaining fame after being prescribed to US president Eisenhower after his heart attack in 1955. As the only available class of oral anticoagulants, vitamin K antagonists (VKA) became the standard for long-term anticoagulant therapy and have been used by many millions of patients.

Although highly effective, the use of VKA is complicated by its narrow therapeutic range and unpredictable pharmacokinetics.[2,3] Due to genetic heterogeneity in VKA metabolism and numerous interactions with food and drugs, treatment with VKA requires periodic monitoring of its anticoagulant effect through the international normalized ratio (INR).[4,5] This monitoring imposes a significant burden on healthcare systems and patients, leading to an underuse of anticoagulants. Furthermore, even with laboratory monitoring, time in therapeutic range is often suboptimal, reducing the benefits of VKA treatment.

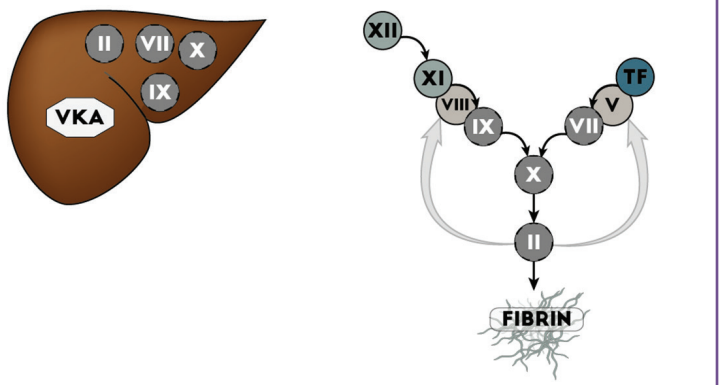
To overcome these challenges, a novel class of direct acting oral anticoagulants has been developed. These non-vitamin K oral anticoagulants (NOACs) or direct-acting oral anticoagulants (DOACs) feature more predictable pharmacodynamic and pharmacokinetic properties compared to VKA.[6] Due to their predictable relation between drug dose and anticoagulant effect, NOACs are designed to be used at a fixed dose, without routine monitoring of coagulation parameters.

In this paper, we aim to give an overview of the pharmacodynamic and pharmacokinetic properties of the NOACs. We will discuss how the efficacy and safety of NOACs compares to VKA for the treatment and prevention of VTE, as well as for the prevention of stroke in patients with atrial fibrillation. Finally, we will discuss the practical use of NOACs in daily practice.

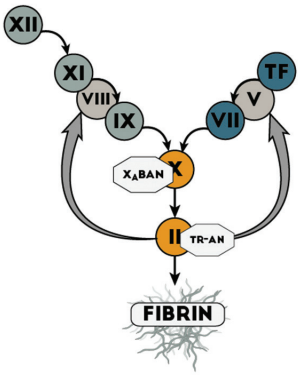
Pharmacodynamics: How do NOACs work?

Four different NOACs are currently approved for VTE treatment and for stroke prevention in AF patients. All 4 NOACs target the common pathway of the coagulation cascade that starts with the activation of clotting factor X, either through the extrinsic or the intrinsic coagulation pathway. Activated factor X (Xa) in turn activates prothrombin to thrombin, which turns soluble fibrinogen into insoluble fibrin strands.

In contrast to VKA, which affects the maturation of different clotting factors (II, VII, IX and X) (Figure 2A), NOACs bind to and inactivate a single activated clotting factor. Rivaroxaban, apixaban and edoxaban are direct factor Xa-inhibitors, whereas dabigatran is a direct thrombin inhibitor (Figure 2B).



Panel A: Vitamin K antagonists (VKA) interfere with the final steps in the hepatic production and maturation of the vitamin K dependent clotting factors, factors II, VII, IX and X. In the presence of VKA, these clotting factors are produced in an inactive form due to a missing gamma-carboxylation. The presence of non-functional factor II, VII, IX and X interferes with the coagulation cascade at different levels, leading to a reduced fibrin generation.



Panel B: In contrast, NOACs are small molecules that bind directly to active clotting factors; either factor Xa (Xa-BAN) for the direct thrombin inhibitors rivaroxaban, apixaban, and edoxaban, or to thrombin (TR-AN), for the thrombin inhibitor dabigatran. This results in a stoichiometric inhibition of the active clotting factors, also reducing downstream fibrin generation.

Figure 2: Comparison of mode of action of vitamin K antagonists (VKA) and Non-vitamin K antagonists Oral Anticoagulants (NOACs).

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All NOACs are non-peptidic small molecules that share a high affinity (Ki in the nanomolar range) and specificity (little effect on other serine proteases) for their respective targets. Dabigatran specifically and reversibly binds to the active site of both free and fibrin-bound thrombin[7]. In contrast with the indirect Xa-inhibitor fondaparinux, the direct Xa-inhibitors bind to the active site of Xa, and inactivate both free Xa and Xa-incoporated in the prothrombinase complex.[8-11]

Due to their direct activity on a single clotting factor, there is a close correlation between the plasma concentrations and the anticoagulant effect of these agents. Because of this predictable pharmacodynamic profile, pharmacokinetic factors are the main determinant of the net anticoagulant effect in a given patient.

Pharmacokinetics: What does the clinician need to know?

The main pharmacokinetic properties and indications for dose adjustment for the NOACs are summarized in Table 1.

Table 1: Pharmacological properties of NOACs

Criteria	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Prodrug	Yes	No	No	No
Bioavailability	6%	90% (with food)	50%	60%
Time to peak levels (hours)	2	2-4	2-4	2
Terminal half-life (hours)	12-14	5-14	13	10-14
Metabolism	Esterase hydrolysis of prodrug for activation CYP-independent glucuronidation	CYP3A4 CYP2J2	CYP3A4 CYP1A2 CYP2C8 CYP2C9 CYP2C19 CYP2J2	<4% CYP3A4
Renal elimination	80%	35%	25%	50%
PgP substrate	Yes	Yes	Yes	Yes
Posology for stroke prevention in AF patients	2x150mg	1x20mg	2x5mg	1x60mg
Dose reduction	2x110mg	1x15mg	2x2.5mg	1x30mg
Criteria for dose reduction	CrCl 30-50ml/min Elderly Increased bleeding risk Concomitant use of verapamil	CrCl 15-50ml/min	serum creatinin 1.5mg/dL and either age ≥80 or body weight ≤ 60kg	CrCl 15-50ml/min Weight ≤ 60kg Concomitant use of cyclosporin, dronedarone, erythromycin, or ketoconazole
Use not recommended	CrCl <30ml/min Concomitant use of PgP-inhibitors ketoconazole, itraconazole, dronedarone, cyclosporin Concomitant use of PgP-inducers rifampicin, carbamazepin, phenytoïn	CrCl <15ml/min Concomitant use of antiretroviral protease inhibitors and azoles (except fluconazole) Concomitant use of PgP-inducers rifampicin, carbamazepin, phenytoïn	CrCl <15ml/min Concomitant use of antiretroviral protease inhibitors and azoles (except fluconazole) Concomitant use of PgP-inducers rifampicin, carbamazepin, phenytoïn	CrCl <15ml/min Concomitant use of PgP-inducers rifampicin, carbamazepin, phenytoïn

CrCl: creatinin clearance; CYP: cytochrome P450 protein; PgP: P-glycoprotein transporter

Absorption and prodrug conversion

Dabigatran

To increase its bioavailability, dabigatran is formulated as a prodrug, dabigatran etexilate. Overall, the bioavailability of dabigatran etexilate remains low (about 6%) and depends on an acid environment. Therefore, dabigatran capsules contain pellets with tartaric acid. To ensure reliable absorption, dabigatran capsules should not be opened or crushed.[12]

Peak plasma concentrations are reached within 2 hours of oral administration. During absorption, dabigatran etexilate is rapidly converted in the active molecule dabigatran through esterase-catalysed hydrolysis in the enterocytes, portal vein, and liver.[13-15] Dabigatran has a relatively low plasma protein binding of approximately 35%, which allows the elimination of dabigatran by hemodialysis.[16]

Xa inhibitors

Compared to dabigatran etexilate, the Xa-inhibitors do not require activation of a pro-drug, and have a higher bio-availability. For apixaban and edoxaban, bio-availability is independent of food intake at about 50% (apixaban) or 60% (edoxaban), whereas the bio-availability of rivaroxaban increases from 65% to > 90% when taken with food.[17-19] Oral absorption is rapid, and peak plasma levels are reached within about 2 hours for edoxaban, and 2-4 hours for rivaroxaban and apixaban.[6] Apixaban and rivaroxaban can be crushed and administered by nasogastric tube without relevant changes in absorption.[17,18] Since Xa-inhibitors have relatively high plasma binding, dialysis is not very effective in reducing plasma levels.

Elimination

Dabigatran

The terminal half-life of dabigatran is around 12-14 hours, and is independent of the dose. About 80% of dabigatran is renally excreted, with the remaining 20% of elimination through conjugation and mainly biliar excretion.[7] Because of the predominantly renal elimination, overall dabigatran exposure depends on the renal function. Patients with moderate or severe renal impairment have a 3- and 6-fold higher plasma AUC of dabigatran compared to patients with normal kidney function. In patients with a creatinine clearance below 30ml/min, half-life increases to over 24 hours[16]; therefore, dabigatran is not indicated in such patients.[20] In elderly patients and patients with a creatinine clearance of 30-50ml/min, a dose reduction of dabigatran is recommended. The elimination rate should also be taken into account when interrupting dabigatran treatment for elective invasive procedures or surgery. In patients with normal renal function (clearance ≥ 80ml/min), it is recommended to stop dabigatran 24 hours prior to most procedures, and 48 hours prior to high-risk procedures or major surgery.[20] In patients with a clearance of 50-80ml/min, this should be increased to 1-2 days (standard procedure) or 2-3 days (high-risk procedure), whereas patients with a clearance below 30ml/min require an interruption of 2-3 days (standard procedure) or 4 days (high-risk procedure) to allow normalization of hemostasis.[20]

Dabigatran is not metabolized by CYP isoenzymes, but is a substrate for the P-glycoprotein transporter (PgP).[7] Therefore, PgP-inhibitors increase dabigatran plasma concentrations. Moderate hepatic impairment did not affect the rate of dabigatran glucoronidation. A study in patients with moderate hepatic impairment (Child-Pugh B) showed similar pharmacokinetics and pharmacodynamics of single-dose administration of dabigatran etexilate compared to matched controls with similar renal function7. Nevertheless, the label restricts the use of dabigatran in patients with hepatic enzymes of >2 times the upper limits of normal, and in patients with hepatic impairment.[12]

Xa-inhibitors

All Xa-inhibitors are partially renally excreted, but to a somewhat variable extent. The contribution of renal elimination in total drug clearance (elimination of unchanged drug) is lower for apixaban (25%) compared to rivaroxaban (35%) and edoxaban (about 50%).[9,17-19,21,22] The terminal half-life of rivaroxaban is 5 to 9 hours in young subjects, and 11-14h in the elderly.[23] For apixaban and edoxaban, mean terminal half-lives are 13 and 10-14h, respectively.[22] Although Xa-inhibitors are less dependent on renal elimination compared to dabigatran, renal impairment also increases the exposure to Xa-inhibitors. Use of direct Xa-inhibitors is currently not recommended in patients with a creatinine clearance below 15ml/min, and should be used with caution in patients with moderate renal impairment if other factors that may increase exposure are present.[20] Furthermore, patients with mild to moderate reduction in renal function should be evaluated for dose reduction (see below).[20]

All Xa-inhibitors undergo hepatic metabolisation. Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms.[24] Apixaban is metabolised mainly via CYP3A4 and also to a lesser extent by CYP1A2, 2C8, 2C9, 2C19 and 2J2.[22,25,26] Edoxaban is approximately 50% hepatically metabolised, but mainly via CYP3A4-independent mechanisms (<4% CYP3A4).[19] Thus, drugs that either induce or compete for CYP-metabolism may influence drug levels (see below). Furthermore, all Xa-inhibitors are substrates of P-glycoprotein. Thus, co-administration of drugs with both CYP3A4 and P-gp inhibition properties (e.g., ketoconazole, ritonavir) with Xa-inhibitors should be avoided as this may reduce their elimination and significantly increase systemic exposure.[20]

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Clinical use of NOACs in VTE

Primary prevention of VTE

The clinical development of all NOACs follows a similar pattern. Clinical trials in the prevention of VTE after major orthopaedic surgery, using a venogram to assess their efficacy in preventing mostly asymptomatic venous thrombosis, is a well-established clinical development model to validate the efficacy and safety of new anticoagulants. The approval of NOACs for the prevention of VTE in orthopaedic patients has preceded other indications; dabigatran, rivaroxaban, apixaban and edoxaban all are approved in some parts of the world for preventing VTE after total knee or hip replacement.

Acute treatment of VTE

When trials have established the efficacy and safety of the NOAC in the prevention of VTE after major orthopaedic surgery, large-scale trials are being initiated for the treatment and secondary prevention of VTE, and for stroke prevention in patients with atrial fibrillation.

The study design and results of the phase III trials with NOACs in VTE treatment are summarized in Table 2.

Table 2: Overview of phase III studies of NOACs in the acute treatment of VTE

Name of study	EINSTEIN-DVT	EINSTEIN-PE	RE-COVER	RE-COVER II	AMPLIFY	HOKUSAI-VTE
NOAC studied	Rivaroxaban	Rivaroxaban	Dabigatran	Dabigatran	Apixaban	Edoxaban
Initial treatment	Rivaroxaban 15mg twice daily	Rivaroxaban 15mg twice daily	LMWH for at least 5 days	LMWH for at least 5 days	Apixaban 10mg twice daily	LMWH for at least 5 days
Continued treatment	Rivaroxaban 20mg once daily	Rivaroxaban 20mg once daily	Dabigatran 150mg twice daily	Dabigatran 150mg twice daily	Apixaban 5mg twice daily no	Edoxaban 60mg once daily
Dose reduction?	no	no	no	no		Yes, 30mg once daily in patients with weight ≤60kg, clearance ≤50ml/min, or treated with potent Pgp-inhibitors
N° of patients	3449	4832	2539	2568	5395	8240
Mean age	56	58	55	55	57	56
% of patients with PE	100	0	31	31	35	40
% of patients with active or recent cancer	6	5	5	4	3	9

The EINSTEIN program investigated the efficacy and safety of rivaroxaban for the treatment of acute DVT (EINSTEIN DVT) and acute PE (with or without symptomatic DVT, EINSTEIN PE), with a total of over 8000 patients width VTE[27]. Rivaroxaban was consistently shown to be non-inferior to standard enoxaparin/VKA therapy for the reduction of recurrent VTE in EINSTEIN DVT and EINSTEIN PE. In the DVT study, there was a trend for a superior efficacy outcome with rivaroxaban compared with enoxaparin/VKA (2.1% vs 3.0%, respectively; HR = 0.68; $p = 0.08$), which was not observed in the PE study (2.1% vs 1.8%; HR=1.12; $p = 0.57$)[28]. In EINSTEIN PE, a significant reduction in major bleeding by 50% was observed in patients receiving rivaroxaban when compared with those receiving enoxaparin/VKA (1.1% vs 2.2%, respectively; HR = 0.49, $p = 0.003$), whereas EINSTEIN DVT showed a 35% reduction in major bleeding with rivaroxaban compared to warfarin that did not reach statistical significance (0.8% vs 1.2%, respectively; HR = 0.65; $p = 0.21$)[29].

The efficacy and safety of a short course of low molecular weight heparin (LMWH) followed by dabigatran has been investigated for the treatment of acute symptomatic VTE in the RE-COVER study program, including over 5,000 patients[30]. Dabigatran showed non-inferiority in the reduction of recurrent VTE compared with warfarin, with a similar safety profile, in a general VTE population, which included patients with DVT (~69%), PE (~21%) and both DVT and PE (~9%) across both treatment arms[30]. The RE-COVER II study confirmed non-inferiority of dabigatran.

The AMPLIFY program compared the use of apixaban with warfarin in over 5,000 patients with VTE. Compared with warfarin, apixaban was as effective in the prevention of recurrent VTE, but was associated with an almost 70% reduction in the risk of major bleeding events[31].

In HOKUSAI VTE, the largest phase III VTE study, LMWH followed by edoxaban was as effective (HR 0.83, 95%CI 0.60-1.14) as well-controlled warfarin in preventing recurrent VTE, with a similar risk of major bleeding[32].

For the clinician, it is important to understand how the design of the studies influences the initial treatment phase of the various NOACs. In the clinical studies with dabigatran and edoxaban, the initial treatment was therapeutic (LMW)heparin, whereas in the clinical trials with rivaroxaban and apixaban, a single drug approach has been investigated with an intensified NOAC regimen for 1 (apixaban) or 3 (rivaroxaban) weeks. Therefore, treatment with rivaroxaban or apixaban can be started with an all-oral regimen, whereas initial parenteral LMWH is required before initiating dabigatran or edoxaban. When starting an all-oral treatment, it is crucial to ensuring a proper switch from the higher initial dose to the lower maintenance dose.

Taken together, these studies have included almost 30,000 patients with acute symptomatic VTE. A meta-analysis of the studies confirms that for the treatment of acute VTE, NOACs are as effective as well-controlled VKA, while offering a 40% reduction in major bleeding (HR 0.61, 95%CI 0.45-0.83) (Figure 3). NOACs are now the preferred treatment choice for the majority of patients with acute VTE. Subgroup analysis showed no difference in efficacy in patients with high vs low bodyweight. In elderly patients and in patients with moderate renal insufficiency, the relative benefit of NOACs was even higher due to a higher relative efficacy of NOACs compared to warfarin[33]. In the approximately 1,500 patients with active or recent cancer who were included in these studies, NOACs were more effective than and at least as safe as warfarin. Nevertheless, guidelines currently still recommend LMWH as a first-line treatment in cancer-related thrombosis, awaiting the results of a head-to-head comparison of LMWH with NOACs. Results of the first of those studies, the HOKUSAI-Cancer study, which compares the use of edoxaban with LMWH in patients with cancer-related VTE, are awaited at the end of 2017.

Long-term secondary prevention of VTE

The efficacy of long-term treatment and secondary prevention of symptomatic VTE with dabigatran was demonstrated in the RE-MEDY and RE-SONATE studies (see Table 3)[30,34].

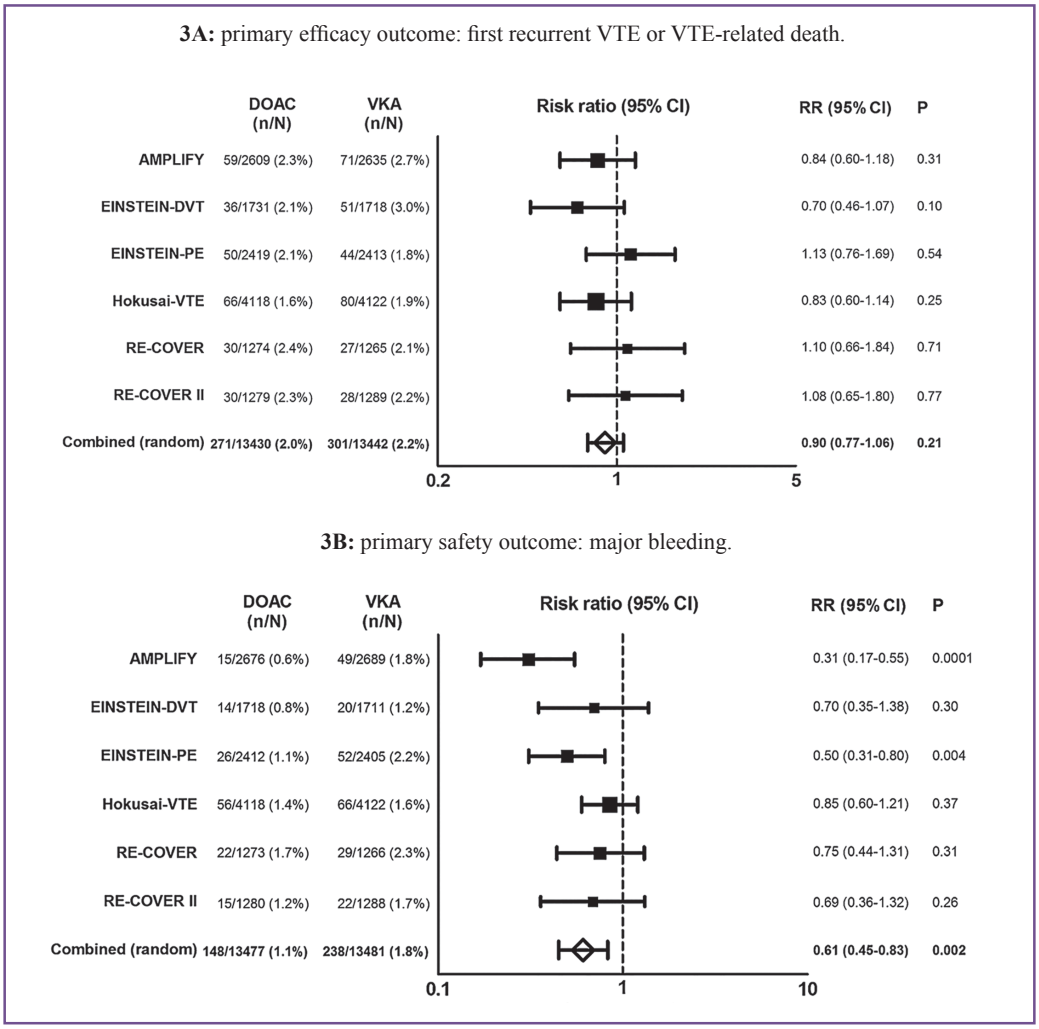

Figure 3: summary of results of phase III trials of NOACs in the treatment of acute VTE.

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Table 3: Clinical trials of new oral anticoagulants and available alternatives in the extended treatment of secondary prevention of VTE: design and summary of results

	Dabigatran		Rivaroxaban		Apixaban	Low dose aspirin	
Trial	RE-MEDY	RE-SONATE	EINSTEIN-extension	EINSTEIN-CHOICE	AMPLIFY-extension	WARFASA	ASPIRE
Dose	150 mg bid	150 mg bid	20mg od	20mg od or 10mg od	2.5 or 5 mg bid	100mg od	100mg od
Comparator	warfarin	placebo	placebo	Low-dose aspirin	placebo	placebo	placebo
Number of patients	2539	1343	1196	3396	2486	403	822
Patient group	3-12 months of treatment completed	6-18 months of treatment completed	6-12 months of treatment completed	6-12 months of treatment completed	6-12 months of treatment completed	first unprovoked VTE, 6-18 months of treatment completed	first unprovoked VTE, 6 weeks-24 months of treatment completed
Treatment duration	6-36 months	6 months	6 or 12 months	12 months	12 months	24 months	24-48 months
Efficacy: recurrent VTE treatment / comparator	1.8% / 1.3%	0.4% / 5.6%	1.3% / 7.1%	1.5% (20mg) 1.2% (10mg) /4.4% (low-dose ASA)	1.7% (2.5mg) 1.7% (5.0mg) /8.8%	6.6%/11.2%(1)	4.8%/6.5%(1)
	HR 1.05 (*p*=0.0001 for non-inferiority)	HR 0.08 (p<0.0001)	HR 0.19 (p<0.0001)	HR 0.34 (20mg) HR 0.26 (10mg)	RR 0.19 (2.5mg) RR 0.20 (5.0mg)	HR 0.58 (p=0.02)	HR 0.74 (p=0.09)
	non-inferior to warfarin	superior to placebo	superior to placebo	Superior to low-dose aspirin	superior to placebo	superior to placebo	trend for superiority compared to placebo
Safety: major bleeding treatment / comparator	0.9% / 1.8%	0.3% / 0.0%	0.7% / 0.2%	0.5% (20mg) 0.4% (10mg) /0.3% (low-dose ASA)	0.2% (2.5mg) 0.1% (5.0mg) /0.5%	0.5%/0.5%	0.6%/0.5%(1)
	HR 0.52 (*p*=0.058)	n/a (no bleeds in placebo group)	no sign different from placebo	no sign different from aspirin	no sign different from placebo	no sign different from placebo	no sign different from placebo
	significantly lower bleeding compared to warfarin	significant increase in bleeding compared to placebo	significant increase in bleeding compared to placebo	Similar bleeding risk as low-dose aspirin	trend for increased bleeding compared to placebo, not significant	no sign different from placebo	no sign different from placebo

VTE: venous thromboembolism; (1) % events per year

Apixaban has been evaluated for the extended treatment in patients who had completed 6 to 12 months of anticoagulation and for whom there was clinical equipoise to continue or to stop anticoagulant Both tested doses (2.5 mg and 5 mg twice daily) were effective in preventing recurrent VTE, without a significant increase in major bleeding complications.[35]

The EINSTEIN Choice compared low-dose aspirin with rivaroxaban in the 'therapeutic' dose (20mg once daily) or the 'prophylactic' dose (10mg once daily) in patients who completed at least 6 months of anticoagulation after an acute VTE event. Importantly, this study confirmed the important residual risk of VTE recurrence after stopping anticoagulant therapy. Patients with unprovoked VTE had a risk of recurrence of more than 5%/yr. after switching from anticoagulation to low-dose aspirin. Both doses of rivaroxaban reduced the risk of recurrence by about 70%, without significantly increasing the risk of major bleeding.[36]

Based on these studies, the use of a lower intensity of anticoagulation seems an effective and safe strategy for the long-term secondary prevention of venous thromboembolism in a large majority of patients. Evidently, a regular re-assessment of the benefits and potential downsides of prolonged anticoagulation is required in patients receiving long-term anticoagulation, with special attention to modifiable risk factors for bleeding.

Clinical use of NOACs in AF

The study design and results of the phase III trials with NOACs in the prevention of stroke and systemic embolism in patients with AF are summarized in Table 4.

Table 4: overview of phase III studies of NOACs in the prevention of stroke and systemic embolism in patients with non-valvular AF

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF
NOAC	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150mg twice daily or 110mg twice daily	20mg once daily	5mg twice daily	60mg once daily or 30mg once daily
Dose reduction?	no	Yes, 15mg once daily if clearance ≤50ml/min	Yes, 2.5mg twice daily if 2 out of three following: Weight ≤60kg Serum creatinine ≥1.5mg/dl Age >80 year	Yes, 50% dose reduction if one or more of following: Weight ≤60kg Clearance ≥50ml/min Treatment with strong Pgp inhibitors
Design	Open label, blinded outcome adjudication	Double blind	Double blind	Double blind
N° of patients	18113	14264	18201	21105
% of patients ≥75 years	36%	40%	35%	39%
% of patients with CHADS2 of ≥3	33%	87%	30%	53%
% of patients with prior stroke or TIA	20%	55%	19%	28%
% of patients with creatinine clearance <50ml/min	19%	21%	17%	19%
Mean TTR in warfarin control group	65%	58%	66%	68%

The landmark trials in the 1990s showed that anticoagulation based on VKA targeted to an INR of 2-3 reduces the risk of stroke in patients with AF by about 65 to 70%, while also reducing mortality.[37,38] However, these studies were relatively small. A new era of anticoagulation was started with the publication of the RE-LY study, the first study of a NOAC, dabigatran, in patients with atrial fibrillation.

The RE-LY was an open-label study with blinded outcome adjudication, randomizing patients with AF and at least one risk factor for stroke to one of three arms: warfarin, dabigatran 110mg twice daily, or dabigatran 150mg twice daily. In terms of efficacy, both doses of dabigatran were at least as effective as warfarin in preventing stroke and systemic embolism, with the higher 150mg bid dose offering a significant reduction in strokes and ischemic events, as well as in ischemic strokes alone, on top of the well-known protective effect of warfarin. Whereas the long-standing concept was that more effective anticoagulation was always balanced with a higher risk of bleeding, both doses of dabigatran were at least as safe, with a significant reduction of major bleeding for the lower (110mg bid) dose of dabigatran. Importantly, the most severe bleeding manifestation of intracranial hemorrhage was strongly and significantly reduced by 70% by both doses of dabigatran.[39]

The ROCKET-AF study showed that a once-daily dose of 20mg of rivaroxaban, reduced to 15mg in patients with a creatinine clearance of below 50ml/min, lowered the risk of the combined endpoint of stroke and systemic embolism compared to warfarin, without increasing the risk of major bleeding. Importantly, this study included a high-risk population: the mean age was 73 years, and 87% of study participants had a CHADS2 score of 3 or more, with more than half of all patients having a prior stroke or TIA.[40]

The ARISTOTLE trial compared warfarin with a twice daily 5mg dose of apixaban, reduced to 2.5mg twice daily if at least two of the following criteria were met: age above 80,

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serum creatinine above 1.5mg/dL, and body weight ≤60kg. This regimen was associated with a 20% reduction of stroke and systemic embolism, a 30% lower risk of major bleeding, and a significant 10% reduction of mortality, compared to warfarin.[41]

Finally, the ENGAGE-AF study randomized over 21,000 patients to warfarin or two different doses of edoxaban: 60 or 30mg twice daily. In each edoxaban arm, the dose was halved in patients who had either a low body weight (≤60kg), a creatinine clearance of below 50ml/min, or who were treated with verapamil, quinidine, or dronedarone. Compared with warfarin, edoxaban 60mg reduced both stroke/systemic embolism and major bleeding by about 20%. The lower, 30mg dose (reduced to 15 mg in patients with the above-mentioned risk factors) was associated with an even larger reduction of major bleeding of more than 50%, and was as effective as warfarin to prevent the combination of stroke or systemic embolism. However, because of an excess of ischemic stroke compared with warfarin (40% increase), the 30mg dose (15mg in patients meeting dose reduction criteria) was not marketed for stroke prevention.[42]

When combined in a meta-analysis, all NOACs show to be at least as effective to prevent stroke or systemic embolism, with a 20% reduction on top of the protection that VKAs had already shown to offer. The reduction in strokes is mainly driven by a dramatic decrease of the anticoagulation-associated risk in hemorrhagic strokes, reduced by more than 50%. (Figure 4)

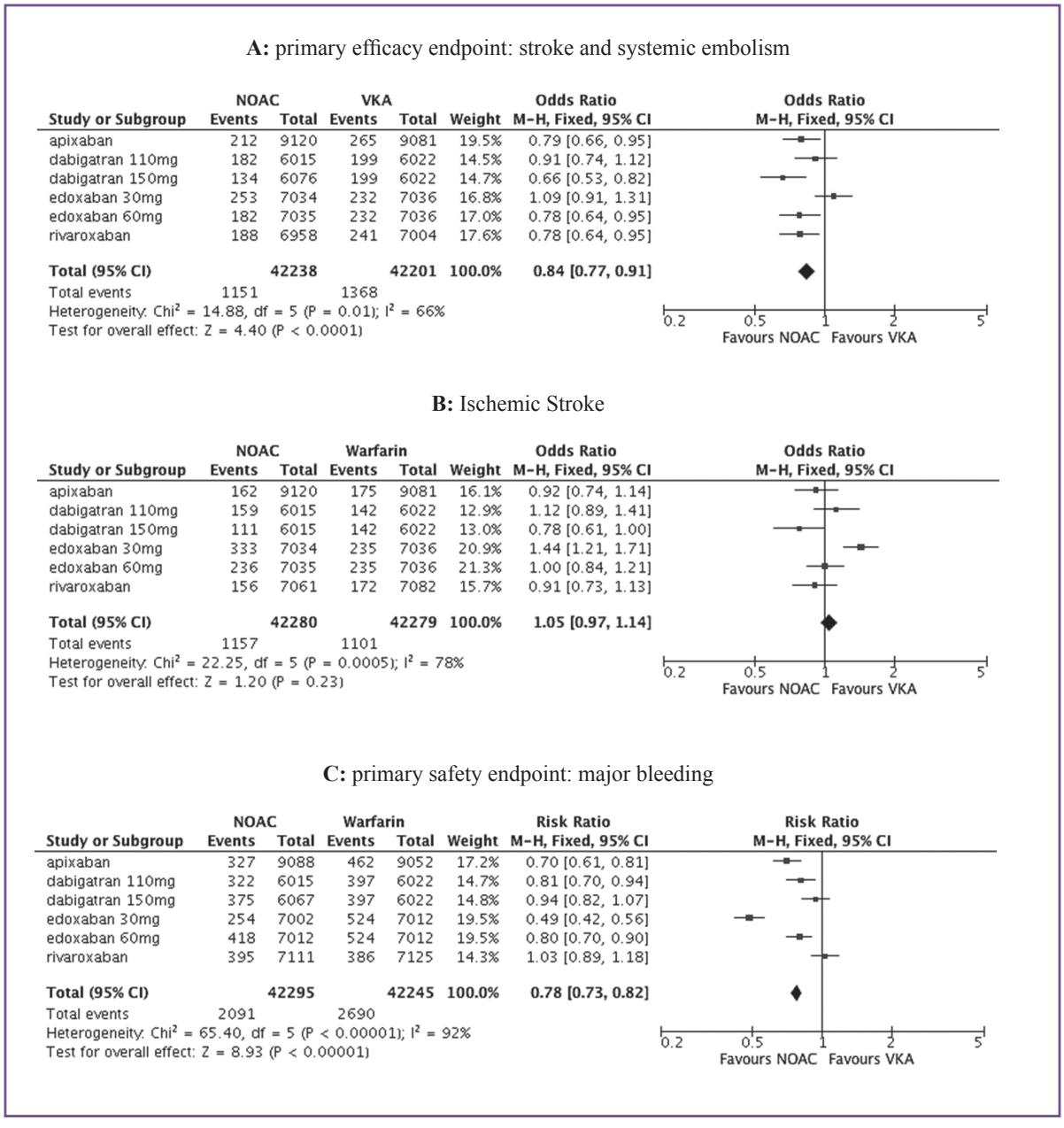

Figure 4: Overview of results of phase III studies of NOACs in the prevention of stroke and systemic embolism in patients with non-valvular AF.

NOACs: less bleeding, but shift in bleeding patterns

When looking at overall bleeding, apixaban, both doses of edoxaban, and the lower dose of dabigatran had significantly lower rates of major bleeding compared to warfarin, with a statistically neutral effect of dabigatran 150mg and rivaroxaban. The magnitude of the reduction ranged from about 20% reduction for edoxaban 60mg and dabigatran 110mg, to a more than 50% reduction for the lower dose of edoxaban. In a pooled analysis, major bleeds were reduced by 20% for DOACs compared to warfarin, with an absolute risk reduction of 0.72% per year.[43] This translates into a NNT of 140, suggesting that for every 140 patients treated with DOACs as opposed to warfarin, one major bleeding episode is prevented (Figure 4C).

All DOACs significantly reduced the incidence of hemorrhagic stroke compared to warfarin, with reductions ranging from 41% (rivaroxaban) to 74% (dabigatran 150mg) (Figure 5). In contrast, there was in increase in GI bleeding compared to warfarin for rivaroxaban and for the higher doses of dabigatran and edoxaban, but not for low-dose dabigatran and apixaban. The only DOAC regimen to reduce GI bleeding was low dose edoxaban[43] (Figure 5).

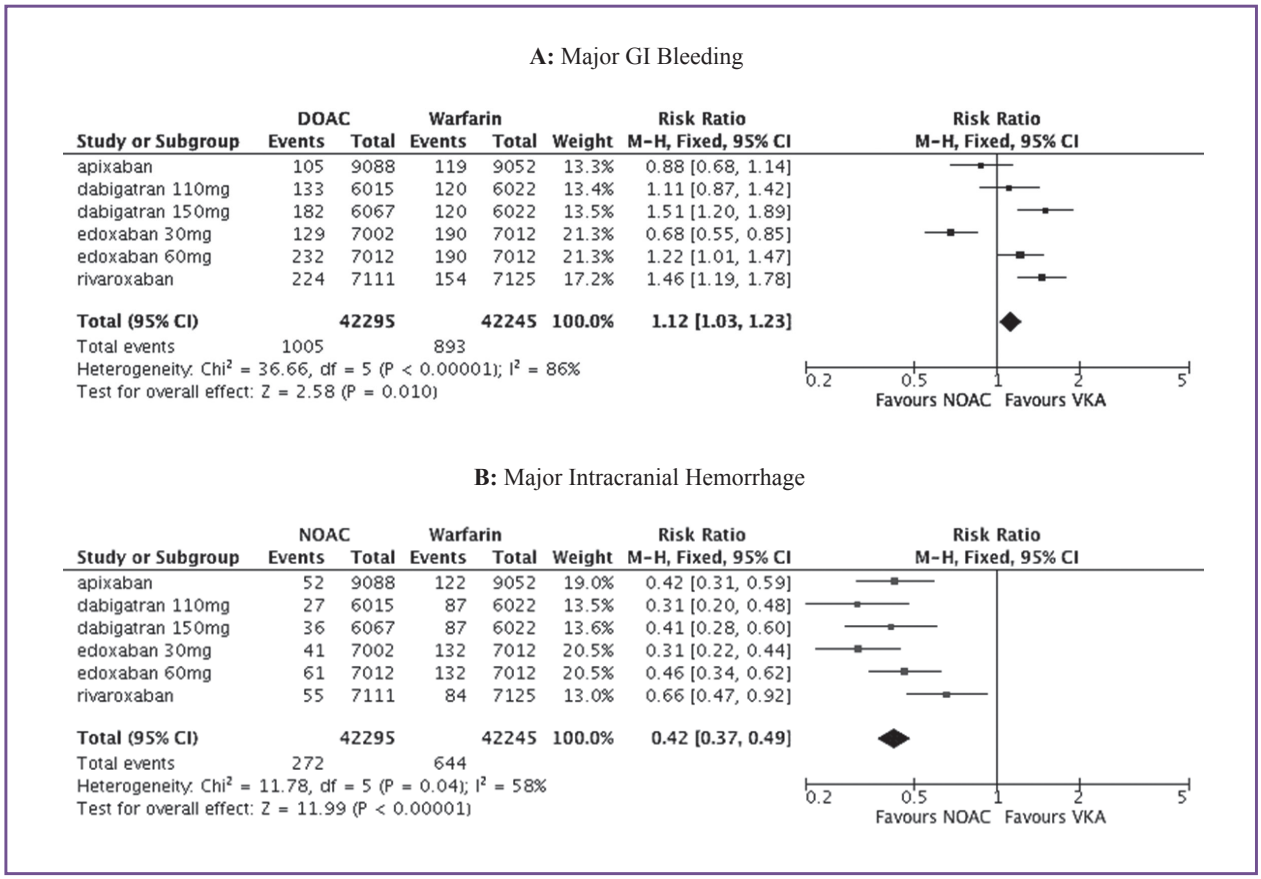

Figure 5: Differences in organ-specific bleeding patterns: major bleeding in GI tract (panel A) vs intracranial hemorrhage (panel B) of NOACs compared to warfarin.

Taken together, these data suggest a clear discrepancy in GI bleeding as compared to overall (major) bleeding, leading to either a higher GI bleeding rate despite a neutral effect on overall major bleeding (dabigatran 150mg, rivaroxaban), a reduction in major bleeding but no impact on GI bleeding (dabigatran 110mg, and apixaban), or a reduction in major bleeding with an increase in GI bleeding (edoxaban 60mg). Only for edoxaban 30mg, GI bleeding and major bleeding were both reduced. One explanation of this finding may be that the direct action of the DOACs combined with high intra-luminal doses due to incomplete absorption lead to increased local anticoagulant activity at the level of the gastro-intestinal wall.

Besides causing fewer bleeds, NOAC-associated bleeding in patients from clinical trials has also been shown to have a better outcome.

Who not to treat with a NOAC?

The large phase III trial programs, both in VTE (almost 30 000 patients) and in AF (over 70 000 patients) have allowed to extensively study important patient subgroups. Although frailer patients have a higher risk of both thrombo-embolic complications as for anticoagulant-related bleeding, overall, the relative benefit of NOACs is most pronounced in frailer

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patients, including patients over 75 years old, and patients with moderately reduced renal function. Importantly, accumulating 'real-world evidence' shows that the outcomes in patients outside clinical trials are very consistent with the findings from those studies, further reassuring clinicians about the favorable risk-benefit profile of NOACs.[43]

However, some important patient groups were not studied in those large clinical trials. Very few patients with a creatinine clearance of below 30ml/min were studied, as this was an exclusion criterium in most of the studies. As all NOACs are partially renally excreted, drug levels are higher in patients with lower creatinine clearance. This is especially true for dabigatran, which is almost exclusively excreted via the kidney (80% renal clearance). Thus, NOAC doses should be adjusted according to the label in patients with moderately reduced kidney function. With proper dose adjustment and careful follow-up of the renal function, NOACs can be used with caution in patients with a creatinine clearance of down to 30ml/min, and down to 15ml/min in selected patients for NOACs with relatively lower renal excretion (apixaban, edoxaban). However, NOACs are contra-indicated in patients with advanced renal failure (creatinine clearance ≤15ml/min) and in dialysis patients.[20]

NOACs cross the placental barrier in animal models, and therefore are contra-indicated in pregnant women. Similarly, based on potential exposure, NOACs should not be used in lactating women.[6,12,17-19]

A single study evaluated the use of dabigatran in patients with mechanical artificial heart valves. As this study showed more thrombotic and more bleeding complications with the treatment regimen studied, NOACs should not be used in patients with mechanical heart valves.[44,45] Importantly, patients with moderate to severe valvular disease, including severe mitral insufficiency and aortic stenosis, were included in the phase III trials. The effects of NOACs were not different in those patients compared to the overall study results. Similarly, NOACs can be safely used in patients who underwent valve replacement surgery with a bioprosthesis, or who had valve repair surgery.

Coagulation monitoring and measurement of anticoagulant effect

Due to the unpredictable pharmacokinetics and narrow therapeutic range, VKA require periodic monitoring of the anticoagulant effect to guide dosing. In contrast, NOACs where developed to be used without routine laboratory monitoring. All phase III clinical trials compared the use of a fixed, unmonitored dose of NOAC with monitored VKA therapy. As discussed elsewhere, these trials showed that the use of a fixed NOAC dosing regimen, adapted to patient characteristics but without any laboratory monitoring, was at least as effective and safe as well-controlled VKA therapy. Furthermore, the relative efficacy and safety of NOACs vs. VKA was consistent regardless of age, body weight, renal function, and frailty. Thus, for the vast majority of patients, measurement of the anticoagulant effect of NOACs is not required for treatment.

Although NOACs in general do not require monitoring, the measurement of NOAC-related anticoagulation may be helpful in some specific situations. First, in patients presenting with bleeding or requiring urgent interventions, a more specific evaluation of the anticoagulant effect can help to guide further treatment. Second, in patients with several factors that may influence NOAC exposure (age, body weight, renal function, and concomitant medication), assessment of NOAC levels could be useful to prevent excess exposure to anticoagulants, which may increase bleeding.

By interfering with the common pathway of anticoagulation (Xa-thrombin), NOACs can prolong clotting times and affect routine coagulation testing. Nevertheless, the effect of different NOACs is variable. Dabigatran prolongs the thrombin time (TT), escarin clotting time (ECT), and the aPTT. An ecarin-based chromogenic assay and a calibrated diluted thrombin time (dTT) provide a highly reliable estimate of dabigatran levels, whereas the aPTT provides an approximative quantification of dabigatran levels, but has limited sensitivity. Dabigatran has little effect on the prothrombin time (PT).[46,47]

Rivaroxaban, in contrast, leads to a dose-dependent prolongation of the PT. However, the sensitivity and the degree of correlation with rivaroxaban plasma levels depends on the reagent used. Rivaroxaban has little effect on the aPTT.[48] The effects of apixaban and edoxaban on standard clotting assays are limited, and routine assays are not very helpful in qualitative or quantitative assessment of plasma levels of either drug.[49,50]

For all Xa-inhibitors, measurement of anti-Xa-activity strongly correlates with drug levels, and a calibrated anti-Xa-assay can be used to quantitatively measure drug levels.[20]

Stopping anticoagulant therapy and reversal of the anticoagulant effect of NOACs

One of the main advantages of NOACs over VKAs is their shorter half-life. In those situations where interruption of anticoagulation is required, simply stopping the administration of the NOAC will result in normalization of the hemostatic system over the following 24 to 48 hours. Importantly, however, due to the renal clearance of NOACs, this time window is longer in patients with reduced kidney function.

For elective interventions that require the interruption of anticoagulation, current guidelines take into account the type of NOAC, the kidney function, and the bleeding risk of the intervention (Table 5).

Table 5: Recommendations for interruption of NOAC therapy for elective surgical interventions: timing of last intake of NOAC

	Dabigatran	Rivaroxaban	Apxaban, Edoxaban, Rivaroxaban	
Creatinine clearance	low bleeding risk*	high bleeding risk	low bleeding risk	high bleeding risk
≥ 80ml/min	≥24h	≥48h	≥24h	≥48h
50-80ml/min	≥36h	≥72h	≥24h	≥48h
30-50ml/min	≥48h	≥96h	≥24h	≥48h
15-30ml/min	Not indicated	Not indicated	≥36h	≥48h
<15ml/min	(use of NOACs not indicated, if patient presents with reduced kidney function, longer interruption may be required prior to elective interventions)			

Note: procedures without increased bleeding risk, or superficial procedures with possibility for adequate local hemostasis: no prior interruption of NOACs required, perform procedure at trough levels (i.e. 12 or 24h after last intake).
** intrinsic risk of bleeding or potential impact in case of bleeding*

In some situations, patients may require more rapid normalization of their hemostatic system, for instance when urgent surgery is required, or in case of major bleeding. When urgent reversal of anticoagulation is warranted, in vitro and in vivo data suggest that prothrombin complex concentrates (PCCs), when given in high dose (50IU/kg), can normalize clotting tests and can reduce blood loss and improve outcome in animal bleeding models.[51]

For dabigatran, a specific humanized monoclonal antibody fragment that binds dabigatran with very high affinity has been developed to specifically neutralize its anticoagulant effects. Idarucizumab, administered in a single 5g dose, immediately and completely neutralized the anticoagulant effect of dabigatran, resulting in a direct and sustained normalization of hemostasis in patients presenting with active bleeding or requiring urgent surgery.[52-54] Idarucizumab has been approved for dabigatran reversal, and is the first choice when urgent reversal of anticoagulation is required in patients treated with dabigatran.[55] Since it specifically targets dabigatran, it has no effect on the anticoagulant effect of VKAs, other NOACs, or heparines.

Andexanet alpha, an inactive factor Xa-analogue, is under development as a reversal agent for Xa-inhibitors, including the NOACs apixaban, rivaroxaban, and edoxaban, as well as the indirect Xa-inhibitors such as heparine and LMWH. A bolus followed by a continuous infusion of andexanet alpha was shown to normalize clotting tests in volunteers treated with direct Xa-inhibitors and in patients presenting with bleeding.[56,57] Regulatory approval is awaited in the upcoming years, pending the results of an ongoing clinical study. Awaiting the availability of a specific reversal agent, PCCs should be considered as hemostatic support in patients who require urgent reversal of direct Xa-inhibitor activity.

Conclusion

The development of oral anticoagulants with a more predictable pharmacokinetic and pharmacodynamics profile has allowed to provide reliable anticoagulation with a fixed once- or twice daily dose without need for drug level monitoring in millions of patients. The efficacy and safety of a fixed-dose NOAC is at least as good, if not better, than dose-adjusted VKA therapy over a wide range of patient's subtypes for the prevention and treatment of VTE and for the prevention of stroke in patients with non-valvular AF. The large clinical study programs, ongoing new trials, and a large body of real-world evidence phase IV studies has increased our knowledge about anticoagulation in specific situations and patient populations, and has improved the quality of therapy with NOACs and VKA alike. Their ease of use, relative safety, and good efficacy has made the NOACs the drug of choice for many patients.

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