

# The Non-Vitamin K Antagonist Oral Anticoagulants in Heart Disease: Section V—Special Situations

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## Abstract

Non-vitamin K antagonist oral anticoagulants (NOACs) include dabigatran, which inhibits thrombin, and apixaban, betrixaban, edoxaban and rivaroxaban, which inhibit factor Xa. In large clinical trials comparing the NOACs with the vitamin K antagonist (VKA) warfarin, dabigatran, apixaban, rivaroxaban and edoxaban were at least as effective for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism, but were associated with less intracranial bleeding. In addition, the NOACs are more convenient to administer than VKAs because they can be given in fixed doses without routine coagulation monitoring. Consequently, the NOACs are now replacing VKAs for these indications, and their use is increasing. Although, as a class, the NOACs have a favourable benefit–risk profile compared with VKAs, choosing among them is complicated because they have not been compared in head-to-head trials. Therefore, selection depends on the results of the individual trials, renal function, the potential for drug–drug interactions and preference for once- or twice-daily dosing.

## Keywords

- oral anticoagulants
- non-vitamin K antagonist oral anticoagulants
- NOACs
- special situations

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In addition, several ‘special situations’ were not adequately studied in the dedicated clinical trials. For these situations, knowledge of the unique pharmacological features of the various NOACs and judicious cross-trial comparison can help inform prescription choices. The purpose of this position article is therefore to help clinicians choose the right anticoagulant for the right patient at the right dose by reviewing a variety of special situations not widely studied in clinical trials.

## Introduction

The non-vitamin K antagonist oral anticoagulants (NOACs), which also are known as the direct oral anticoagulants, include the direct thrombin inhibitor dabigatran, and the direct factor Xa (FXa) inhibitors apixaban, betrixaban, edoxaban and rivaroxaban. In large clinical trials comparing the NOACs with the vitamin K antagonist (VKA) warfarin four NOACs, namely, dabigatran, apixaban, rivaroxaban and edoxaban, were at least as effective for stroke prevention in atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE), but were associated with less intracranial bleeding.<sup>1,2</sup> Another oral FXa inhibitor, betrixaban, has been favourably compared with the low molecular weight heparin (LMWH) enoxaparin for extended thromboprophylaxis in medically ill patients. In general, the NOACs are more convenient to administer than other anticoagulants because they can be given orally in fixed doses without routine coagulation monitoring, have fewer drug interactions than the VKAs and their activity is not influenced by dietary vitamin K intake. Consequently, the NOACs are now replacing VKAs for most indications in which they were tested.

Although, as a class, the NOACs have a favourable benefit-risk profile compared with VKAs, choosing among them is complicated by the fact that there are no head-to-head comparative trials. Therefore, selection depends on the results of the individual trials, renal function, the potential for drug–drug interactions and preference for once- or twice-daily dosing. The purpose of this position article is to help clinicians choose the right anticoagulant for the right patient at the right dose. We here therefore review pertinent data to facilitate the choice of the right anticoagulant for patients in a few selected ‘special situations’, and summarize current evidence for the efficacy and safety of the various NOACs to provide practical guidance. This review is meant to complement the European Heart and Rhythm Association Practical Guide on NOACs.<sup>3</sup>

This review concludes a series of position papers dedicated to the use of anticoagulants in heart disease that were commissioned under the aegis of the European Society of Cardiology Working Group on Thrombosis. Previous papers in this series covered: New oral anticoagulants in AF and acute coronary syndromes<sup>4</sup>; Blood coagulation and targets of anticoagulants – Section I;<sup>5</sup> Parenteral anticoagulants – Section II<sup>6</sup>; Vitamin K antagonists – Section III<sup>7</sup>; and Oral anticoagulants in coronary heart disease – Section IV.<sup>8</sup>

## Indications and Contraindications for the NOACs

Except for betrixaban, the NOACs are approved for prevention of stroke in AF,<sup>9–12</sup> for initial, long-term and extended treatment of VTE<sup>13–20</sup> and for prevention of VTE after elective hip or knee replacement.<sup>21–27</sup> For the latter indication, however, edoxaban is only licensed in Japan. Finally, low-dose rivaroxaban (2.5 mg twice daily) is approved in Europe, but not in North America, for prevention of recurrent ischaemic events in stabilized acute coronary syndrome patients. This dose of rivaroxaban is now also approved in the European Union, and is under consideration by regulatory bodies in North America for use in conjunction with aspirin to reduce the risk of cardiovascular death, myocardial infarction and stroke in patients with stable coronary or peripheral artery disease.

The most recently approved NOAC is betrixaban, which is licensed in North America for extended thromboprophylaxis in high-risk medically ill patients. Its approval in other countries is pending.<sup>28</sup> Therefore, the indications for the NOACs vary from country to country.

The recommended NOAC dosing regimens and criteria for dose reduction are different across indications, which adds to the complexity of NOAC management (► **Table 1**).<sup>29–34</sup> In particular, the dosing regimens for rivaroxaban and apixaban vary across the continuum of care in patients with VTE. Therefore, frequent patient follow-ups are imperative to ensure that these dose transitions occur in clinical practice. Unlike the randomized trials for stroke prevention in AF, there were no dose reduction criteria for rivaroxaban or apixaban in the VTE trials. For acute treatment of VTE, dabigatran and edoxaban were studied after a minimum 5-day course of treatment with a parenteral anticoagulant (► **Table 1**). In contrast, rivaroxaban or apixaban were administered without a heparin lead-in, which simplifies transition of care from the emergency department to home.

Compared with VKAs, NOACs have fewer drug interactions, and dietary vitamin K has no impact on their metabolism. Nonetheless, at doses of 15 or 20 mg, rivaroxaban needs to be taken with food to maximize absorption. The absorption of dabigatran etexilate depends on an acid micro-environment, which is maintained by the tartaric acid core of the dabigatran etexilate pellets found within the capsules.<sup>3</sup>

All of the NOACs are substrates for P-glycoprotein (P-gp). Consequently, potent P-gp inhibitors can increase drug exposure, whereas potent P-gp inducers can reduce it. These

**Table 1** NOACs dosing recommendations by approved indication

Stroke prevention in atrial fibrillation		
Drug	Dose	Dose reduction criteria
Dabigatran <sup>29,30</sup>	150 mg twice daily if CrCl > 30 mL/min	Outside U.S.: 110 mg twice daily if age ≥80 y or concomitant verapamil U.S. specific: 110 mg dose is not available; 75 mg twice daily if CrCl 15–30 mL/min or if CrCl 30–50 mL/min with potent P-gp inhibitor dronedarone or ketoconazole
Apixaban <sup>32</sup>	5 mg twice daily	2.5 mg twice daily if ≥2 of the following: age ≥80 y, weight ≤60 kg, creatinine ≥1.5 mg/dL
Rivaroxaban <sup>31</sup>	20 mg once daily with evening meal if CrCl > 50 mL/min	15 mg once daily with the evening meal if CrCl 15–50 mL/min
Edoxaban <sup>33</sup>	60 mg once daily if CrCl > 50 mL/min; U.S. 60 mg once daily if CrCl > 50 to ≤95 mL/min	30 mg once daily if CrCl 15–50 mL/min, weight ≤60 kg or potent P-gp inhibitor
Treatment of deep venous thrombosis or pulmonary embolism		
Dabigatran <sup>29,30</sup>	150 mg twice daily following 5–10 d initial parenteral anticoagulant	Outside U.S.: 110 mg twice daily if age ≥80 y or concomitant verapamil
Apixaban <sup>32</sup>	10 mg twice daily for 7 d followed by 5 mg twice daily	None
Rivaroxaban <sup>31</sup>	15 mg twice daily with food for the first 21 d followed by 20 mg per d	None
Edoxaban <sup>33</sup>	60 mg once daily following 5–10 d of initial therapy with parenteral anticoagulant	30 mg once daily following 5–10 d of initial therapy with parenteral anticoagulant if CrCl 15–50 mL/min, weight ≤60 kg or potent P-gp inhibitor
Prevention of recurrent deep venous thrombosis or pulmonary embolism		
Dabigatran <sup>29,30</sup>	150 mg twice daily	Outside U.S.: 110 mg twice daily if age ≥80 y or concomitant verapamil
Apixaban <sup>32</sup>	2.5 mg twice daily	None
Rivaroxaban <sup>31</sup>	10 mg once daily with or without food after at least 6 mo standard therapy	None
Prevention of venous thromboembolism following hip or knee replacement surgery		
Dabigatran <sup>29,30</sup>	110 mg orally first day, then 220 mg once daily if CrCl > 30 mL/min	150 mg once daily if CrCl 30–50 mL/min, concomitant verapamil, amiodarone, quinidine, age ≥75 y
Apixaban <sup>32</sup>	2.5 mg twice daily	None
Rivaroxaban <sup>31</sup>	10 mg once daily with or without food	None
Prevention of venous thromboembolism in the medically ill		
Betrixaban <sup>34</sup>	Initial single dose of 160 mg, followed by 80 mg once daily, taken with food	Initial single dose of 80 mg followed by 40 mg once daily if CrCl ≥ 15 to < 30 mL/min or concomitant P-gp inhibitor
Prevention of recurrent ischaemia following acute coronary syndrome		
Rivaroxaban <sup>31</sup>	2.5 mg twice daily (not approved in the U.S.)	

Abbreviations: CrCl, creatinine clearance; NOAC, non-vitamin K antagonist oral anticoagulant; P-gp, P-glycoprotein.

interactions mandate dose reduction when NOACs are administered with certain drugs, and *tout-court* drug avoidance with others (►Table 2). Unlike dabigatran and edoxaban, rivaroxaban and apixaban are metabolized by cytochrome P450 3A4 (CYP3A4), which necessitates additional potential drug avoidance recommendations. The clinical relevance of most of these pharmacological interactions remains unclear. Nonetheless, they need to be considered, and drug dosages

should be adjusted according to their labels and to guidelines until more data are accrued.<sup>3</sup>

The NOACs have many advantages over VKAs. These include the convenience of fixed dosing without the need for routine coagulation monitoring, and the lower risk of serious bleeding, particularly intracranial haemorrhage. Nonetheless, important caveats remain. Although the risks of fatal and intracranial bleeding were lower with the NOACs

**Table 2** Specific considerations and treatment recommendations

Drug	Recommendations
Dabigatran <sup>29,30</sup>	<p>Reduce dose if CrCl 30–50 mL/min or with a strong P-gp inhibitor (dronedarone, ketoconazole); avoid strong P-gp inducers (e.g. rifampin)</p> <p>Patients with elevated liver enzymes &gt; 2 ULN were excluded in the trials. Use in such conditions is not recommended</p> <p>Contraindicated if CrCl &lt; 30 mL/min</p> <p>No data for use in pregnancy or lactation; APS; AF and cancer; contraindicated in mechanical heart valve or moderate to severe mitral stenosis</p>
Apixaban <sup>32</sup>	<p>For patients receiving 5 or 10 mg twice daily, reduce the dose by 50% if co-administered with strong dual inhibitors CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin); avoid co-administration if prescribed 2.5 mg dose</p> <p>Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (e.g. rifampin, carbamazepine, phenytoin, St. John's wort)</p> <p>Dosing recommendations cannot be provided for patients with moderate hepatic impairment (Child-Pugh class B); not recommended in patients with severe hepatic impairment (Child-Pugh class C)</p> <p>CrCl &lt; 25 mL/min excluded from trials</p> <p>No data for use in pregnancy or lactation; APS; AF and cancer; contraindicated in mechanical heart valve or moderate to severe mitral stenosis</p>
Rivaroxaban <sup>31</sup>	<p>Avoid concomitant use with dual P-gp and strong CYP3A4 inhibitors (e.g. ketoconazole and ritonavir)</p> <p>Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (e.g. rifampin, carbamazepine, phenytoin, St. John's wort)</p> <p>Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy</p> <p>CrCl &lt; 30 mL/min excluded from trials</p> <p>No data for use in pregnancy or lactation; APS; AF and cancer; contraindicated in mechanical heart valve or moderate to severe mitral stenosis</p>
Edoxaban <sup>33</sup>	<p>Avoid use with rifampin</p> <p>Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B and C)</p> <p>Avoid use if CrCl &lt; 15 mL/min</p> <p>No data for use in pregnancy or lactation or APS; contraindicated in mechanical heart valve or moderate to severe mitral stenosis</p>
Betrixaban <sup>34</sup>	<p>Reduce dose with concomitant use of P-gp inhibitors (e.g. amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin)—initial single dose of 80 mg followed by 40 mg once daily</p> <p>Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B and C)</p> <p>Reduce dose if severe renal impairment (CrCl ≥ 15 to &lt; 30 mL/min)—initial single dose of 80 mg followed by 40 mg once daily</p> <p>Avoid use if severe renal impairment coupled with P-gp inhibitor</p> <p>No data for use in pregnancy or lactation; APS; contraindicated in mechanical heart valve or moderate to severe mitral stenosis</p>

Abbreviations: AF, atrial fibrillation; APS, anti-phospholipid antibody syndrome; CrCl, creatinine clearance; CYP, cytochrome P-450; P-gp, P glycoprotein; ULN, upper limit of normal.

than with VKAs, the risk of gastrointestinal bleeding was higher with several of the NOACs. NOACs are contraindicated in patients with mechanical heart valves.<sup>35</sup> NOACs also are contraindicated in AF patients with rheumatic heart disease associated with severe mitral stenosis because such patients were excluded from the phase 3 trials comparing NOACs with warfarin. However, ongoing trials are comparing NOACs with VKAs in AF patients with rheumatic heart disease.<sup>36,37</sup>

In addition, the NOACs are contraindicated in patients with severe renal impairment, as evidenced by a creatinine clearance (CrCl) of less than 15 mL/min, as assessed by the Cockcroft–Gault formula (eCrCl); VKAs remain the standard of care for these patients. Although NOACs are licensed for use in patients with an eCrCl between 15 and 30 mL/min, there are limited efficacy and safety data in such patients because the trials excluded patients with an eCrCl < 30 mL/min (< 25 mL/min

for apixaban) (► **Table 2**). Theoretically, however, the use of NOACs in place of VKAs in patients with severe renal impairment may reduce the risk of vascular calcification<sup>38</sup>—which increases the risk of cardiovascular complications—and parenchymal microbleeds with excessive anticoagulation—which can lead to renal tubular obstruction by red blood cell casts.<sup>39</sup> Therefore, more information about the efficacy and safety of the NOACs is needed in this vulnerable population, in which the evidence for the effectiveness of VKAs is limited. Trials are underway to test some of the NOACs in dialysis patients.

All of the NOACs are metabolized to some extent in the liver. Consequently, patients with moderate-to-severe hepatic dysfunction, defined as Child-Pugh class B or C,<sup>40</sup> were excluded from the randomized trials. The lack of evidence supporting the use of NOACs in this complex patient population is problematic, as VKA use has been associated with harm. Therefore, such patients have few options for anticoagulant therapy.

Finally, NOACs are contraindicated in pregnancy and in nursing mothers, and data for their use in the paediatric population are limited. Although the doses of some NOACs are reduced in patients with low body weight, this is not universal, and the efficacy, safety and optimal dose of the NOACs in patients with very high body weights are uncertain. These uncertainties and others have prompted interest in measuring plasma levels of the NOACs in some situations. Such conditions are addressed below.

## Laboratory Monitoring of the NOACs: When and How

Although routine monitoring of the NOACs is not required, measurement of plasma concentrations may be useful in certain situations to: (1) assess their contribution to serious bleeding and identify appropriate patients for reversal; (2) determine optimal timing of urgent surgery; (3) to identify patients with acute ischaemic stroke who can safely receive fibrinolytic therapy; and (4) detect under- or over-exposure in patients with risk factors such as drug interactions, extremes of weight or renal function and drug omission or overdose (► **Table 3**). Assays that measure drug levels are more informative than global tests of coagulation. Quantitative assays include the diluted thrombin time (TT) or ecarin clotting time or chromogenic assay for the determination of the plasma levels of dabigatran; and anti-FXa assays for the oral FXa inhibitors. Unfortunately, quantitative assays are not available in all hospitals in a rapid turnaround format.<sup>3</sup> The ability to measure the anticoagulant effects or the levels of the NOACs is useful for the appropriate management of these patients and for the correct identification of patients requiring reversal.

Global coagulation assays, such as the activated partial thromboplastin time (aPTT) and the prothrombin time (PT)/international normalized ratio are readily accessible in clinical practice, and the TT is available in many hospitals. Consequently, these tests are often used as screening tests to provide timely information on the presence or absence of an anticoagulant effect of a NOAC<sup>41</sup> (► **Table 4**). However, routine coagulation assays are limited by the variable reagent-dependent responsiveness to NOACs and their inability to quantify

NOAC levels. Nonetheless, a normal TT excludes the presence of clinically relevant concentrations of dabigatran. If the TT is unavailable, a normal aPTT may be useful, a concept supported by the fact that there are several reports of dabigatran-treated patients with a normal aPTT, particularly those in whom the last dose of dabigatran was taken more than 24 hours previously, who have safely received thrombolytic therapy for an acute ischaemic stroke.<sup>42</sup> If there is doubt about residual anticoagulant effects of dabigatran, endovascular thrombectomy is another option.

For oral FXa inhibitors, the PT is more responsive to the anticoagulant effects of rivaroxaban and edoxaban than the aPTT, whereas neither the PT nor the aPTT is responsive to apixaban. Unlike the TT and possibly the aPTT, a normal PT does not exclude clinically relevant concentrations of any of the oral FXa inhibitors.

Quantitative assays for measuring NOAC levels might be preferred over global coagulation assays, but access to such tests is limited (► **Table 5**). The gold standard is liquid chromatography tandem mass spectrometry (LC-MS/MS), but this is not routinely available. Instead, dedicated coagulation assays with specific drug calibrators are recommended for the measurement of NOAC levels. These dedicated assays generally demonstrate good agreement with LC-MS/MS in validation studies, and have the advantage of being easily adapted to existing diagnostic platforms. Dedicated clot-based assays, such as the diluted TT and the ecarin clotting time, or chromogenic assays are recommended for measuring dabigatran levels; whereas chromogenic anti-FXa assays are the tests of choice to quantify the levels of the oral FXa inhibitors, such as apixaban, edoxaban, rivaroxaban or betrixaban.<sup>41</sup>

Because of the short half-lives of the NOACs and their partial renal clearance, it is important to determine the timing of blood sampling relative to the last intake of the drug and renal function. Although therapeutic ranges and validated safe cut-offs for drug levels are lacking to assess the adequacy of dosing, the optimal timing for surgery, the need for reversal agents or the suitability for systemic thrombolysis, interpretation of drug levels is facilitated by the availability of trough and peak on-therapy ranges derived from pharmacokinetic analyses in NOAC trials<sup>32,43–45</sup>; and of a safe threshold for surgery (< 30 ng/mL) proposed by various professional societies<sup>46,47</sup> (► **Table 6**).

## Reversal of the NOACs—When and How

Bleeding is the major complication of anticoagulant therapy. Although NOACs are associated with less severe bleeding than VKAs<sup>48,49</sup> and their short half-life renders reversal unnecessary in many situations, rapid reversal is desirable in patients with life-threatening bleeding or in those requiring urgent surgery.

### Dabigatran Reversal

#### Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with high affinity (► **Table 7**)

**Table 3** When and why to measure NOAC levels

When?	Why?
Life-threatening or major bleeding	To identify contribution of NOACs to bleeding To identify the need to administer a reversal agent
Urgent procedure/surgery	To determine safety to proceed to surgery
Thrombolysis	To determine safety to proceed to thrombolysis
Recurrent thromboembolism	To distinguish under-exposure, non-adherence and drug failure
Clinical characteristics pre-disposing to extreme drug levels: e.g. extremes of weight, age, renal function	To detect under- or over-exposure
Potential drug interactions	To detect under- or over-exposure
NOAC overdose	To detect overdose, and inform on the risk period for bleeding

Abbreviation: NOAC, non-vitamin K antagonist oral anticoagulant.

**Table 4** Responsiveness of routine coagulation assays

Assays	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	++	+	+	+
PT	+	++	+	++
TT	+++	No effect	No effect	No effect

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; PT, pro-thrombin time; TT, thrombin time. Note: + = poorly responsive, ++ = moderate responsive, +++ = highly responsive. The responsiveness of the aPTT and PT are highly dependent on the thromboplastin reagents used. Dabigatran: A normal TT excludes the presence of dabigatran. In the absence of other causes, a prolonged aPTT in a patient taking dabigatran indicates its presence but a normal aPTT does not always exclude clinically relevant anticoagulant levels; Rivaroxaban and edoxaban: PT is more responsive than aPTT. In the absence of other causes, a prolonged PT in a patient taking one of these DOACs indicates its presence but a normal PT does not exclude clinically relevant anticoagulant levels; Apixaban: Neither PT nor aPTT is responsive.

and rapidly reverses its anticoagulant effects.<sup>50</sup> When administered to dabigatran-treated patients with severe bleeding or needing urgent surgery in the RE-VERSE AD study, an intravenous bolus of 5 g of idarucizumab rapidly corrected abnormal coagulation tests (diluted TT, ecarin clotting time

and aPTT), and produced sustained reductions in the levels of unbound dabigatran for up to 24 hours<sup>51</sup> (►Table 8). In evaluable patients with serious bleeding ( $n = 301$ ), the median time to bleeding cessation was 2.5 hours. Patients with intracranial bleeds were not evaluated for the timing to bleeding cessation. Patients requiring urgent procedures ( $n = 202$ ) underwent them within 1.5 hours of receiving idarucizumab and surgical haemostasis was judged normal in 93.4% of patients, and mildly abnormal in most of the case.<sup>51,52</sup> If the diluted TT or aPTT remain elevated 15 minutes after idarucizumab administration, a second dose can be given. Likewise, if there is re-bleeding or if bleeding fails to stop, a second dose can be considered. In RE-VERSE AD, this only occurred in 3 patients who had renal failure at the time of severe bleeding.<sup>52</sup> If bleeding continues despite normalization of coagulation tests, a search for the cause of bleeding should be undertaken.

#### Other Reversal Strategies

If idarucizumab is unavailable, coagulation factor concentrates (activated pro-thrombin complex concentrate [aPCC] or 3- or 4-factor pro-thrombin complex concentrates [3FPCC or 4FPCC]) may be administered at doses of 25 to 50 units/kg for severe dabigatran-related bleeding based on limited evidence in humans<sup>53–58</sup> (►Tables 8 and 9). There

**Table 5** Quantitative assays for NOACs

Anticoagulants	Assay methods	Principle	Assays/Calibrators
<b>Direct thrombin inhibitor:</b> Dabigatran	Chromogenic  Clot-based	Thrombin-based Ecarin-based Thrombin-based	Hyphen Biomed, Biophen DTI Stago ECA-II Hyphen Biomed HTI, HemosIL DTI, Technoclott DTI, Roche Dilute Thrombin Time, Siemens, INNOVANCE DTI
<b>Direct factor Xa inhibitors:</b> Rivaroxaban, apixaban and edoxaban	Chromogenic	Factor Xa based	Hyphen, Stago, Technoclone, STA-liquid Xa

Abbreviations: DTI, direct thrombin inhibitor; ECA, ecarin chromogenic assay; HTI, hemoclot thrombin inhibitor; NOAC, non-vitamin K antagonist oral anticoagulant; Xa, factor Xa.



**Table 6** Range of NOAC levels observed in clinical trials of atrial fibrillation

NOACs	Dabigatran <sup>43</sup>	Rivaroxaban <sup>44</sup>	Apixaban <sup>163</sup>	Edoxaban <sup>45</sup>
Dose	150 mg bid	20 mg daily	5 mg bid	60 mg daily
<b>C<sub>peak</sub> levels</b>				
Median; ng/mL	184	290	171	170
[range of levels between quoted centiles] <sup>a</sup>	[10th–90th] 74.3–383	[5th–95th] 177–409	[5th–95th] 91–321	N/A
<b>C<sub>trough</sub> levels</b>				
Median; ng/mL	93	32	103	36.1
[range of levels between quoted centiles] <sup>a</sup>	[10th–90th] 39.8–215	[5th–95th] 5–155	[5th–95th] 41–230	[25th–75th] 19.4–62.0

Abbreviations: bid, twice daily; C<sub>peak</sub>, peak plasma level; C<sub>trough</sub>, trough plasma level; NOAC, non-vitamin K antagonist oral anticoagulant.

<sup>a</sup>Range of levels between quoted centiles as reported in either phase II or phase III clinical trials for stroke prevention in atrial fibrillation.

is a risk of thrombotic complications with these agents, particularly with aPCC. Haemodialysis removes dabigatran (up to 60% with a 4- to 6-hour session) and is an option in patients with severe renal dysfunction if idarucizumab is unavailable.<sup>59,60</sup>

### Oral FXa Inhibitor Reversal

#### Andexanet Alfa

Andexanet alfa was recently licensed by the U.S. Food and Drug Administration (FDA), but not yet by other regulatory agencies. Andexanet alfa is a recombinant variant of human FXa that binds and sequesters FXa inhibitors<sup>61</sup> (►Table 7). Andexanet alfa rapidly reversed the anti-FXa activity measured in volunteers given apixaban or rivaroxaban.<sup>62</sup> Furthermore, in apixaban- or rivaroxaban-treated patients with severe bleeding, an andexanet alfa bolus followed by a

2-hour infusion rapidly reduced anti-FXa activity by 93% for apixaban and by 89% for rivaroxaban (►Table 8), but there was a rebound increase in anti-FXa activity 4 hours after the infusion stopped.<sup>63</sup> Nonetheless, haemostasis was adjudicated as good/excellent in 79% of evaluable patients 12 hours after andexanet alfa administration. In volunteers given andexanet alfa, there were transient elevations in D-dimer and pro-thrombin fragment 1 + 2, but the clinical significance of these findings is uncertain.<sup>62</sup> There are currently no clinical data on the use of andexanet alfa for the reversal of oral FXa inhibitors in patients requiring urgent surgery or interventions. In addition, because andexanet alfa also reverses heparin, its use prior to cardiac surgery or coronary interventions procedures where heparin is used routinely may be problematic.

The FDA has now approved andexanet alfa for the reversal of rivaroxaban and apixaban in patients with life-threatening

**Table 7** Characteristics of NOAC reversal agents

	Idarucizumab (aDabi-Fab, BI655075)	Andexanet Alfa (PRT064445)	Ciraparantag (aripazine, PER977)
Type of molecule	Humanized monoclonal antibody fragment	Recombinant modified factor Xa molecule lacking catalytic and membrane binding activity	Synthetic, cationic molecule
Mechanism of action	Non-competitive binding to dabigatran (high affinity)	Competitive binding to factor Xa inhibitors	Non-covalent hydrogen bonding and charge–charge interaction
Anticoagulants reversed	Dabigatran	Direct (apixaban, rivaroxaban, edoxaban) and indirect (low molecular weight heparin) factor Xa inhibitors	Dabigatran, apixaban, rivaroxaban, edoxaban, low molecular weight heparin, unfractionated heparin
Dosing	5 g IV administered as 2 doses of 2.5 g given 15 minutes apart	Apixaban or rivaroxaban (> 7 h post-dose): 400 mg IV bolus and 480 mg infusion Rivaroxaban (< 7 h post-dose), edoxaban, enoxaparin: 800 mg IV bolus and 960 mg infusion	100 to 300 mg IV bolus
Storage	Refrigerated	Refrigerated	Room temperature

Abbreviations: IV, intravenous; NOAC, non-vitamin K antagonist oral anticoagulant.

**Table 8** Published studies of NOAC reversal agents and pro-haemostatic agents in NOAC-treated patients requiring urgent reversal

Study	Patients	Intervention	Efficacy	Thrombosis and mortality
RE-VERSE AD <sup>51</sup>	Dabigatran-treated patients  Group A ( <i>n</i> = 301): uncontrolled bleeding (GI, <i>n</i> = 137; ICH, <i>n</i> = 98; other, <i>n</i> = 166)  Group B: needing urgent invasive procedure ( <i>n</i> = 202)	Idarucizumab 5 g IV (2 doses of 2.5 g)	<u>Reversal of anticoagulation:</u> - Median maximum percentage reversal of abnormal dTT or ECT at 4 h: 100% (95% CI, 100–100) - Unbound dabigatran concentrations less than 20 ng/mL for 24 h in 77% of patients  <u>Haemostasis:</u> - Group A: median time to cessation of bleeding 2.5 h (95% CI, 2.2–3.9) - Group B: normal surgical haemostasis (judged by attending surgeon) in 93.4% of patients	Thrombotic events: - 30 d: <i>n</i> = 24 (4.8%)  - 90 d: <i>n</i> = 34 (6.8%)  Mortality at 30 d: - Group A: <i>n</i> = 19 (13.5%)  - Group B: <i>n</i> = 16 (12.6%)
ANNEXA-4 <sup>a</sup> (NCT02329327)	Apixaban- or rivaroxaban-treated patients with acute major bleeding ( <i>n</i> = 67; GI, <i>n</i> = 33; ICH, <i>n</i> = 28; other, <i>n</i> = 6)	Apixaban or rivaroxaban (> 7 h post-dose): 400 mg IV bolus and 480 mg infusion  Rivaroxaban (< 7 h post-dose): 800 mg IV bolus and 960 mg infusion	<u>Reversal of anticoagulation:</u> Median reduction in anti-FXa activity 89% (95% CI, 58–94) for rivaroxaban-treated and 93% (95% CI, 87–94) for apixaban-treated patients  <u>Haemostasis adjudicated by committee using pre-specified criteria:</u> Good/excellent in 79% (95% CI, 64–89) 12 h post-administration	Thrombotic events at 30 d: <i>n</i> = 12 (18%)  Mortality at 30 d: <i>n</i> = 10 (15%)
Schulman et al <sup>63,74</sup>	Dabigatran-treated patients with major bleeding ( <i>n</i> = 14; GI, <i>n</i> = 5; ICH, <i>n</i> = 5; other <i>n</i> = 4)	aPCC (50 units/kg) as per hospital protocol	<u>Haemostatic efficacy assessed by the treating physician:</u> - Good: <i>n</i> = 9 (64%) - Moderate: <i>n</i> = 5 (36%)  - Poor: <i>n</i> = 0 (0%)	Thrombotic events at 30 d: <i>n</i> = 0 (0%)  Mortality at 30 d: <i>n</i> = 1 (8%)
Majeed et al <sup>73</sup>	Apixaban- and rivaroxaban-treated patients with acute and active major bleeding ( <i>n</i> = 84; GI, <i>n</i> = 13; ICH = 59; other = 12)	4FPCC 1,500 units for weight < 65 kg, 2,000 units for weight > 65 kg (approximate dose 25 units/kg) as per hospital protocol	<u>Haemostatic efficacy assessed by 2 physicians:</u> Effective: <i>n</i> = 58 (69%) Ineffective: <i>n</i> = 26 (31%)	Thrombotic events at 30 d: <i>n</i> = 3 (4%) Mortality at 30 d: <i>n</i> = 27 (32%)

Abbreviations: 4FPCC, 4-factor pro-thrombin complex concentrate; aPCC, activated pro-thrombin complex concentrate; CI, confidence interval; dTT, dilute thrombin time; ECT, ecarin clotting time; FXa, factor Xa; GI, gastrointestinal; ICH, intracranial haemorrhage; IV, intravenous; NOAC, non-vitamin K antagonist oral anticoagulant.

<sup>a</sup>Interim analysis.



**Table 9** Studies of pro-thrombin complex concentrate administered in vivo to NOAC-treated human volunteer subjects

Study	Design	Subjects (n)	NOAC	Treatments	PT	PTT, TT, ECT	Anti-Xa	Thrombin generation assay			Peak thrombin	Other
								LT	TTP	ETP		
Eerenberg et al <sup>53</sup>	Randomized, double-blind, placebo-controlled, crossover	12	Dabigatran 150 mg twice daily × 2.5 d Rivaroxaban 20 mg twice daily × 2.5 d	4FPCC (50 units/kg)								
				Placebo								
Levi et al <sup>66</sup>	Randomized, open-label, placebo-controlled	35	Rivaroxaban 20 mg twice daily × 4.5 d	4FPCC (50 units/kg)						After 12 h		
				3FPCC (50 units/kg)						After 8 h		
Barco et al <sup>70</sup>	Randomized, double-blind, placebo-controlled, crossover	6	Rivaroxaban 15 mg twice daily × 5 doses	4FPCC (25 units/kg)						After 12–24 h		
				4FPCC (37.5 units/kg)						After 6 h		
Cheung et al <sup>69</sup>	Randomized, double-blind, placebo-controlled, crossover	6	Apixaban 10 mg twice daily × 3.5 d	4FPCC (25 units/kg)						After 12–24 h		
				4FPCC (37.5 units/kg)						After 6 h		
Nagalla et al <sup>71</sup>	Randomized, single-blind, placebo-controlled, crossover	12	Apixaban 5 mg twice daily × 5 doses	4FPCC (25 units/kg)								
Zahir et al <sup>67</sup>	Randomized, double-blind, placebo-controlled, crossover	110	Edoxaban 60 mg × 1 dose	4FPCC (10 units/kg)								Normalization of bleeding duration after punch biopsy
				4FPCC (25 units/kg)								
Brown et al <sup>68</sup>	Randomized, double-blind, placebo controlled	24	Edoxaban 60 or 180 mg × 1 dose	3FPCC (25 units/kg)								
				3FPCC (50 units/kg)								

Abbreviations: 3FPCC, 3-factor pro-thrombin complex concentrate; 4FPCC, 4-factor pro-thrombin complex concentrate; aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; ETP, endogenous thrombin potential; LT, lag time; NOAC, non-vitamin K antagonist oral anticoagulant; PCC, pro-thrombin complex concentrate; PT, pro-thrombin time; TT, thrombin time; TTP, time to peak thrombin generation.

Note: Colour boxes indicate the following:

	= No significant effect		= Partial correction		= Complete correction		= Not assessed
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or uncontrolled bleeding. Andexanet also reverses the anticoagulant effects of edoxaban and betrixaban in volunteers. Edoxaban-treated patients were included in the ANNEXA 4 study, but the results have not yet been released. Betrixaban is only licensed for thromboprophylaxis in the United States and reversal is unlikely to be needed with prophylactic doses of the drug. Although not yet licensed for reversal of these agents, it would be reasonable to administer andexanet alfa if patients taking these agents presented with serious bleeding.

### Ciraparantag

Ciraparantag (PER977, aripazine) is a synthetic, cationic molecule under development as a global anticoagulant reversal agent. It binds a variety of anticoagulants, including heparin and all of the NOACs, through non-covalent hydrogen bonding and ionic interactions.<sup>64</sup> Ciraparantag rapidly reduced the prolonged whole blood clotting times in volunteers given a single 60-mg dose of oral edoxaban or a single

1.5-mg/kg subcutaneous injection of enoxaparin.<sup>65</sup> Ongoing studies (NCT03172910, NCT03288454) are evaluating ciraparantag in volunteers given apixaban, rivaroxaban or edoxaban.

### Non-Specific Reversal Agents

In case specific reversal agents are not available, it is reasonable to administer 25 to 50 units/kg of 3FPCC, 4FPCC or aPCC to patients with severe bleeding (along with maximum supportive measures) (►Tables 8 and 9), although their efficacy, safety and optimal dosing are uncertain<sup>53,66–71</sup> and at least one study has reported that PCC is of little or no benefit in patients with NOAC-associated intracranial haemorrhage.<sup>72</sup> Nonetheless, small prospective observational studies suggest that PCC may have some benefit.<sup>73,74</sup>

In summary, idarucizumab is widely available for dabigatran reversal in patients with life-threatening bleeding or in patients requiring urgent surgery. Andexanet alfa is approved by the FDA and will be available soon; but until

andexanet alfa or ciraparantag is available, 3FPCC or 4FPCC should be administered for reversal of oral FXa inhibitors in patients presenting with life-threatening bleeding. Although data supporting their use are limited, recent cohort studies suggest that they improve haemostasis in many patients.<sup>73,74</sup> The net clinical gain associated with specific reversal agents is uncertain.

### Personalizing NOAC Treatment in AF: Are Biomarkers Useful to Individualize Treatment?

AF is associated with a hypercoagulable state, as evidenced by documented abnormalities in markers of coagulation, fibrinolysis, platelet activation, inflammation and extracellular matrix turnover.<sup>75</sup> Biomarkers reflecting these processes have been used to understand the pathophysiology of thrombosis in AF and some have been used as surrogates for efficacy when evaluating various antithrombotic drug regimens.

Biomarkers have also been used for risk stratification in AF patients because the risks of stroke, bleeding or death are not homogeneous, and some biomarkers have prognostic value for different types of events.<sup>75</sup> The concept of using a biomarker to refine clinical risk stratification was proposed over a decade ago when the levels of plasma von Willebrand factor (VWF) were used to help predict stroke risk,<sup>76</sup> so that only those at the highest risk could be targeted for anticoagulation therapy with VKAs. With the advent of the NOACs, which are more convenient and safer than VKAs, the need for such risk stratification is less pressing.<sup>1</sup>

Refined biomarker-based scores have been developed to aid in the prediction of the risks of stroke, bleeding or death in AF patients,<sup>77–79</sup> and recent European guidelines suggest their possible use.<sup>80</sup> Indeed, risk stratification based solely on clinical factors has only modest value in identifying high-risk patients (*c*-index of ~0.60). In every scenario, clinical risk scores could be enhanced by including biomarkers, which can be measured in the blood (e.g. VWF, creatinine, estimated glomerular filtration rate [eGFR] or eCrCl, or proteinuria), and by cardiac or brain imaging (e.g. transthoracic or transoesophageal echocardiography looking at the atrial size, atrial slow flows or left atrial appendage velocities, and/or computed tomography [CT] or magnetic resonance imaging [MRI] of the brain, looking at lesions indicating previous brain embolization). The addition of such biomarkers may increase the *c*-indexes to approximately 0.65,<sup>78</sup> or even higher by including more and more of them in predictive models. However, the practical application of these scores for risk stratification in the era of the NOACs is uncertain, and comes at the cost of simplicity and applicability. Additionally, in a cohort study that included 1,361 AF patients optimally anticoagulated with VKAs, adding high-sensitivity troponin T, N-terminal pro-brain-type natriuretic peptide, interleukin 6, VWF, eGFR and time in therapeutic range increased the predictive value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for cardiovascular events, but not the predictive value of the HAS-BLED score for major bleeding.<sup>81</sup> Reclassification

analyses did not show prediction improvement by adding multiple biomarkers, and the clinical usefulness and net benefit over current clinical scores were modest. Likewise, adding measurements of VWF to the CHA<sub>2</sub>DS<sub>2</sub>-VASc or HAS-BLED scores improved their predictive value, but had minimal impact on the *c*-indices.<sup>82</sup> In essence, the addition of multiple measurements to current scores statistically improves prediction for some endpoints, but the increments are small and have little impact—at least at the moment—on clinical decision making.

Additional uncertainties about the use of risk prediction scores utilizing biomarkers come from studies in anticoagulated patients with AF followed long term. Here, the age, biomarkers, clinical history (ABC)-stroke score was not significantly better than the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>83</sup> In the first 'real-world' validation, the clinical factor-based HAS-BLED score outperformed the ABC-bleeding score for predicting major bleeding, gastrointestinal bleeding and the composite of gastrointestinal bleeding and intracranial haemorrhage.<sup>84</sup> In the era of NOACs, when the focus is on 'whom to treat' and not 'whether to treat', the challenge is to identify the truly low-risk patients who do not warrant anticoagulation treatment.<sup>85</sup> It is currently uncertain whether biomarkers will help with this task,<sup>85</sup> which is problematic because their use adds cost and reduces the simplicity and practicality of the current bedside risk scoring systems.

### Personalizing NOAC Treatment in VTE: Are Biomarkers Useful to Individualize Treatment Duration?

The optimal duration of anticoagulant treatment after a first episode of VTE remains uncertain. Patients with VTE provoked by major transient risk factors, such as surgery or trauma, are usually treated for 3 months, whereas those with unprovoked VTE or VTE provoked by major persistent risk factors, such as cancer or severe thrombophilia, are often treated indefinitely.<sup>86</sup> The decision to extend anticoagulation therapy beyond 3 months should be individually tailored, and requires balancing the risk of recurrence if treatment is stopped with the risk of bleeding if treatment is continued. Patient preferences also need to be considered.<sup>87</sup>

Several strategies have been proposed to help identify patients at high risk for recurrent VTE who may benefit from extended anticoagulant treatment. These include ultrasound evidence of residual thrombosis in patients with deep vein thrombosis (DVT),<sup>88</sup> persistent right ventricular dysfunction in patients with pulmonary embolism (PE)<sup>89</sup> and elevated levels of biomarkers, particularly D-dimer despite anticoagulation treatment or after anticoagulation treatment is stopped.

Despite promising early reports, ultrasound evidence of residual thrombus is not a particularly helpful predictor of recurrence, because up to 50% of DVT patients have this finding. Likewise, anticoagulation is unlikely to be stopped in PE patients with persistent right ventricular dysfunction, because such a finding may identify those with chronic thromboembolic pulmonary hypertension. Therefore, attention has shifted to biomarkers such as D-dimer.

D-dimer levels have been incorporated into several risk prediction models, including the Vienna score, the Males Continue and HERDOO2 rule, as well as the DASH and DAMOVES scores (►Table 10),<sup>90–94</sup> the last three of which have been recently validated.<sup>95–97</sup> Compared with a normal D-dimer level, an elevated D-dimer level measured on treatment or 1 month after stopping anticoagulation therapy is associated with about a twofold increased risk of recurrence. The risk of recurrence in men is twofold higher than that in women. This has led to the recommendation that, regardless of whether the D-dimer is normal or elevated, most men with unprovoked VTE should receive extended anticoagulation therapy unless their risk of bleeding is high. In contrast, discontinuation of anticoagulation may be considered in women with a normal D-dimer, particularly if other risk factors for recurrence, such as advanced age, high body mass index or evidence of post-thrombotic syndrome, are absent.<sup>98</sup>

For extended anticoagulation therapy in VTE patients, the thromboprophylactic doses of rivaroxaban or apixaban (10 mg once daily and 2.5 mg twice daily, respectively) were found to be as effective as the treatment doses (20 mg once daily and 5 mg twice daily, respectively).<sup>19,20</sup> In addition, both the thromboprophylactic and the treatment doses of rivaroxaban were more effective than aspirin at preventing recurrent VTE, and were not associated with significantly higher rates of major bleeding. Therefore, with the convenience and safety of the NOACs, particularly with low-dose rivaroxaban or apixaban, it is likely that more patients with unprovoked VTE will be given extended anticoagulation therapy, irrespective of the currently used biomarkers.

The clinical utility of other biomarkers, such as attenuated fibrinolysis,<sup>99</sup> altered fibrin clot structure<sup>100</sup> or markers of endothelial dysfunction, including low concentrations of soluble E-selectin and high concentrations of soluble intercellular adhesion molecule 1,<sup>101</sup> remains to be determined.

## Peri-Procedural Management of the NOACs

Peri-procedural management is simpler with NOACs than with VKAs because the NOACs have a more rapid onset and offset of action. Bridging is not needed with the NOACs, and low-risk procedures can safely be performed without interrupting treatment. The approach to peri-procedural NOAC management depends on the procedure, as detailed below.

### Surgery

Interruption of the NOACs is unnecessary prior to minor surgical procedures, such as dental cleaning, simple dental extractions, cataract surgery or skin biopsy. Nonetheless, it may be prudent to delay the morning dose until after the procedure, so as to avoid undertaking the procedure when drug levels are at peak.

NOAC treatment should be interrupted prior to procedures associated with a moderate or high risk of bleeding, and the summaries of product characteristics provide guidance for each agent (►Tables 11 and 12). In patients requiring urgent surgery, measurement of drug levels may be helpful.<sup>102,103</sup> For dabigatran-treated patients, reversal

with idarucizumab is suggested if the drug level exceeds 50 ng/mL. For the oral FXa inhibitors, it is still uncertain, despite the claims, as to whether they can be effectively reversed with 4FPCC. After the procedure, full doses of the NOACs should only be restarted when haemostasis is established because—unlike VKAs—the NOACs have a rapid onset of action (see ►Tables 11 and 12). However, in most patients, thromboprophylaxis can be started in the morning of the first post-operative day and continued until full-dose treatment with NOACs is resumed.

### Cardiac Procedures

NOACs can be used in place of VKAs for anticoagulation prior to and after electrical cardioversion for AF.<sup>104–107,166</sup> Provided that compliance is assured, the use of NOACs in patients undergoing cardioversion streamlines care by obviating the need for the coagulation monitoring that is required if VKAs are used, and possibly shortening the time to the procedure by ensuring reliable time with full anticoagulation. Cardiac device implantation or AF ablation<sup>108,109</sup> is considered minor surgery, and can be done without NOAC interruption. In contrast, NOACs must be discontinued for at least 48 hours prior to cardiac surgery.

In anticoagulated AF patients undergoing percutaneous coronary intervention, NOACs are preferable to VKAs. Here, lowering the dose of rivaroxaban from 20 to 15 mg once daily or the dose of dabigatran from 150 to 110 mg twice daily in the setting of 'triple therapy' and early discontinuation of aspirin after the procedure appears to reduce the risk of bleeding without an obvious increase in thrombotic risk,<sup>110,111</sup> although the trials were under-powered for efficacy (►Table 13). It is likely that diagnostic angiography can be safely performed under a NOAC, without discontinuation and without the use of additional heparin.

## The NOACs in Extremes of Body Weight

There are limited efficacy and safety data with the NOACs in patients with extremes of body weight. Since the volume of distribution of the NOACs is related—although not uniquely—to body weight (and with its correlates, surface body area and body mass index), extremes in body weight may affect their efficacy or safety.<sup>112</sup> In general, increased bleeding rates are observed in VTE patients weighing < 50 kg, and mortality in these patients is higher than in those weighing 50 to 100 kg.<sup>113</sup> However, this difference is confounded by the presence of underlying conditions such as cancer, which is also associated with an increased risk of recurrent VTE and bleeding.<sup>113</sup> At the opposite end of the spectrum of body weight, reduced anti-thrombotic effectiveness may occur in patients with high body weights.

A comprehensive summary of the current evidence of NOAC efficacy, safety and requirements for dose adjustment, as derived from the official summary of product characteristics of the individual NOACs, is presented in ►Table 14.<sup>114</sup>

Patients with body weights below 60 kg were less represented in clinical trials than those with high body weights (i.e., < 10% vs >15% of the study population, respectively).<sup>115</sup>

**Table 10** Risk prediction models in venous thromboembolism

Prediction model	Study design and patients	Items	Points	Low risk of recurrence	Status
Vienna prediction score <sup>164</sup>	Prospective cohort 929 patients	Male gender Proximal DVT Pulmonary embolism D-dimer (continuous value on VKAs)	NA	≤180 points (according to nomogram): 4.4% (95% CI, 2.7–6.2)	Derived and validated
HERDOO2 <sup>95</sup>	Prospective cohort 646	Signs of post-thrombotic syndrome D-dimer > 250 µg/L Body mass index ≥30 kg/m <sup>2</sup> Age ≥65 y	1 1 1 1	≤1 point: 1.6% (95% CI, 0.3–4.6)	Derived and validated
DASH tool <sup>92</sup>	Patient level meta-analysis 1,818	D-dimer (normal/abnormal post-VKAs) Age (quartiles) Male gender Hormone therapy	2 1 1 2	≤1 point: 3.1% (95% CI, 2.3–3.9)	Derived and validated
DAMOVES score <sup>94,97</sup>	Prospective cohort 646	Age (decades) Male gender Body mass index ≥30 kg/m <sup>2</sup> Elevated D-dimer during anticoagulation Elevated factor VIII levels Thrombophilia Varicose veins	NA	≤ 11.5 (according to a nomogram): 2.9% (95% CI, 2.13–4.35)	Derived and validated

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; NA, not available; VKA, vitamin K antagonist.

In the individual trials, the efficacy and safety of the NOACs in patients with low body weight appears to be consistent with the overall findings, such that dose reduction solely on the basis of body weight is only required for edoxaban. With apixaban, a body weight of 60 kg or less is only an indication for dose reduction if the patient is 80 years of age or older or has a serum creatinine over 133 µmol/L (1.5 mg/dL). Although it may be prudent to measure drug levels in patients with extremes of body weight, there is currently no guidance on how or when to dose adjust in such patients.<sup>115</sup>

When the NOACs were compared with VKAs in the AF and VTE studies, there were no significant differences in the efficacy or safety of the NOACs in obese patients compared with those with lower body weights. Despite some pharmacokinetic and pharmacodynamic changes in obese patients,

fixed doses of NOACs are recommended in this population without an upper body weight limit. A meta-analysis in VTE patients<sup>116</sup> indicates that the efficacy and safety of the NOACs relative to the VKAs is maintained in patients with a body weight of > 100 kg. However, because few patients with extremes of body weight (i.e., < 50 kg or > 150 kg) were included in the trials, the efficacy and safety of the NOACs in such patients are uncertain, and we advise against their use in most cases.

### NOAC Management in AF Patients with Acute Ischaemic or Haemorrhagic Stroke

The management of anticoagulants in patients suffering an acute ischaemic or haemorrhagic stroke is particularly

**Table 11** Pre-operative management and post-operative restart of dabigatran

Pre-operative emergent	Idarucizumab two boluses of 2.5 g each
Pre-operative elective surgery	Discontinuation according to renal function
Post-operative	Restart as fast as possible provided the clinical situation allows and adequate haemostasis has been established (also after reversal). Patients at risk for bleeding or patients at risk of over-exposure, notably patients with moderate renal impairment (CrCl, 30–50 mL/min) should be treated with caution

Abbreviation: CrCl, creatinine clearance.

**Table 12** Pre-operative discontinuation and post-operative restart of the oral FXa inhibitors

Agent	Discontinuation (h)	Restart
Rivaroxaban	24	As soon as possible provided the clinical situation allows and adequate haemostasis has been established
Apixaban	48 (HBR)	As soon as possible provided the clinical situation allows and adequate haemostasis has been established
	24 (LBR)	As soon as possible provided the clinical situation allows and adequate haemostasis has been established
Edoxaban	24	As soon as possible provided the clinical situation allows and adequate haemostasis has been established. Note that the time to onset of the edoxaban anticoagulant therapeutic effect is 1–2 h. If oral medicinal products cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant and then switch to oral once daily

Abbreviations: FXa, factor Xa; HBR, high bleeding risk; LBR, low bleeding risk.

problematic because of the delicate balance between the risk of bleeding if treatment is continued and the risk of a further ischaemic stroke if treatment is stopped.

### Initiation of Anticoagulation in AF after a Transient Ischaemic Attack or an Ischaemic Stroke

Patients with AF are at risk of thromboembolic events, including acute transient ischaemic attack (TIA) or ischaemic stroke. Patients with acute events were excluded from the trials comparing the NOACs with warfarin for stroke prevention in AF patients. The highest risk of recurrent stroke is in the first 2 weeks after the first event. However, if anticoagulation is started too early in patients with moderate or severe stroke, the risk of bleeding into the ischaemic area is high.<sup>117</sup> At present, there is limited information about the optimal timing for starting oral anticoagulation therapy after a TIA or ischaemic stroke because the phase 3 trials excluded

patients who sustained strokes < 2 weeks previously (with the exception of apixaban in the ARISTOTLE trial, which excluded patients who sustained strokes < 1 week previously).<sup>118–120</sup> Expert opinion suggests starting anticoagulation in patients with a TIA on day 1, in patients with a mild stroke on day 3 and in patients with a moderate stroke on day 6. In patients with a severe stroke, anticoagulation can be initiated after 2 weeks provided that repeat CT of the brain does not show major haemorrhagic transformation<sup>121</sup> (► Fig. 1), but this is not based on any trial data. Ongoing registries and randomized trials will eventually address this question.

### Secondary Stroke Prevention in Patients with AF

All studies comparing the NOACs with warfarin in AF patients included a subgroup of patients with a prior TIA or ischaemic stroke, while excluding patients with prior

**Table 13** Ischaemic events and major bleeding with NOACs in randomized warfarin-controlled trials with cardiac procedures

Procedure	Agent	Ischaemic events (n)			Major bleeding (n)		
		NOAC	VKA	HR	NOAC	VKA	HR
Electrocardioversion <sup>104–106</sup>	Rivaroxaban	5/978	5/492	0.50 (0.15–1.73)	6/988	4/499	0.76 (0.21–2.67)
	Edoxaban	5/1095	11/1,104	0.46 (0.12–1.43)	16/1,067	11/1,082	1.48 (0.64–3.55)
Catheter ablation <sup>108,109</sup>	Rivaroxaban	0/124	2/124	n.a.	0/123	0/121	n.a.
	Dabigatran	5/317	22/318	n.a.	5/317	22/318	0.22 (0.08–0.59)
PCI <sup>110,111</sup>	Rivaroxaban 2.5 <sup>a</sup>	36/704	36/695 <sup>b</sup>	0.93 (0.59–1.48)	117/706	163/697 <sup>b</sup>	0.63 (0.50–0.80) <sup>d</sup>
	Rivaroxaban 15 <sup>c</sup>	41/694	36/695 <sup>b</sup>	1.08 (0.69–1.68)	109/696	163/697 <sup>b</sup>	0.59 (0.47–0.76) <sup>d</sup>
	Dabigatran 110 <sup>e</sup>	108/981	83/981 <sup>b</sup>	1.30 (0.98–1.73)	151/981	264/981 <sup>b</sup>	0.52 (0.42–0.63) <sup>f</sup>
	Dabigatran 150 <sup>e</sup>	60/763	60/764 <sup>b</sup>	0.97 (0.68–1.37)	154/763	196/764 <sup>b</sup>	0.72 (0.58–0.88) <sup>f</sup>

Abbreviations: HR, hazard ratio + 95% confidence intervals; n.a., not available; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

<sup>a</sup>mg b.i.d. plus P2Y<sub>12</sub> blocker and aspirin.

<sup>b</sup>Warfarin, P2Y<sub>12</sub> blocker and aspirin (triple therapy).

<sup>c</sup>mg qd plus P2Y<sub>12</sub> blocker without aspirin.

<sup>d</sup>*p* < 0.001 superiority.

<sup>e</sup>mg, b.i.d. plus P2Y<sub>12</sub> blocker without aspirin.

<sup>f</sup>*p* < 0.001 non-inferiority.

**Table 14** Official recommendations for extreme body weight dosing for the non-vitamin K antagonist oral anticoagulants

	Lower body weight limit allowed in the SmPC	Upper body weight limit allowed in the SmPC	Body weight-based recommendations for dose adjustments in AF	Warnings	Reference	Additional recommendations (Authors' opinions)
Dabigatran etexilate	50 kg	110 kg	No dose adjustment necessary	The safety and efficacy in children from birth to less than 18 y of age have not yet been established. Limited data are available in patients < 50 kg. Very limited clinical experience of dabigatran use in patients weighing > 110 kg	29	
Rivaroxaban	None	None	No dose adjustment necessary	The safety and efficacy in children aged 0–18 y have not been established. Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary	31	Consider further dose reduction in case of eCrCl < 50 mL/min or concomitance with P-gp competition or CYP3A4 inhibition – (demanding a first step of dose reduction see SmPC) and body weight < 50 kg
Apixaban	None	None	Dose reduction necessary in patients weighing < 60 kg when another risk factor (sCr ≥ 1.5 mg/dL or age ≥ 80 y) is present	The safety and efficacy in children and adolescents below age 18 have not been established. Low body weight (< 60 kg) may increase haemorrhagic risk. Compared with apixaban exposure in subjects with body weight of 65–85 kg, body weight > 120 kg was associated with ~30% lower exposure	32	Special warning if two other criteria for dose reduction are met in addition to body weight < 60 kg
Edoxaban	None	None	Dose reduction necessary in patients weighing ≤ 60 kg	The safety and efficacy in children and adolescents less than 18 y of age have not been established. The exposure of edoxaban was found to potentially increase in patients with a body weight ≤ 60 kg. No data on upper limits of body weight for which reliable exposure data are available	33	Warning for obese patients in whom the likelihood of eCrCl > 95 mL/min is higher ('edoxaban should only be used in patients with NVAf and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk')

Abbreviations: AF, atrial fibrillation; eCrCl, estimated creatinine clearance; NVAf, non-valvular atrial fibrillation; P-gp, P glycoprotein; sCr, serum creatinine; SmPCs, summary of product characteristics.



### Initiation or Resumption of Anticoagulation in Patients with Transient Ischaemic Attack or Stroke (1-3-6-12 Day Rule)

Time to re-initiation depends on infarct size: 1 – 3 – 6 – 12 day rule				
Clinical Presentation	TIA	Mild Stroke	Moderate Stroke	Severe Stroke
CT or MRI	Exclude Cerebral Haemorrhage	Small Infarct	Medium Infarct	Large Infarct
Timing of Anticoagulation (days)	1	3	6	12

**Fig. 1** The 1-, 3-, 6- and 12-day rule (the Diener's rule) to guide the resumption of anticoagulation after an ischaemic stroke. Abbreviations: CT, computerized tomography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale. Adapted from Huisman et al.,<sup>161</sup> after Diener, with the author's permission. \*Mild = NIHSS score < 8; moderate = NIHSS score 8–16; severe = NIHSS score > 16.

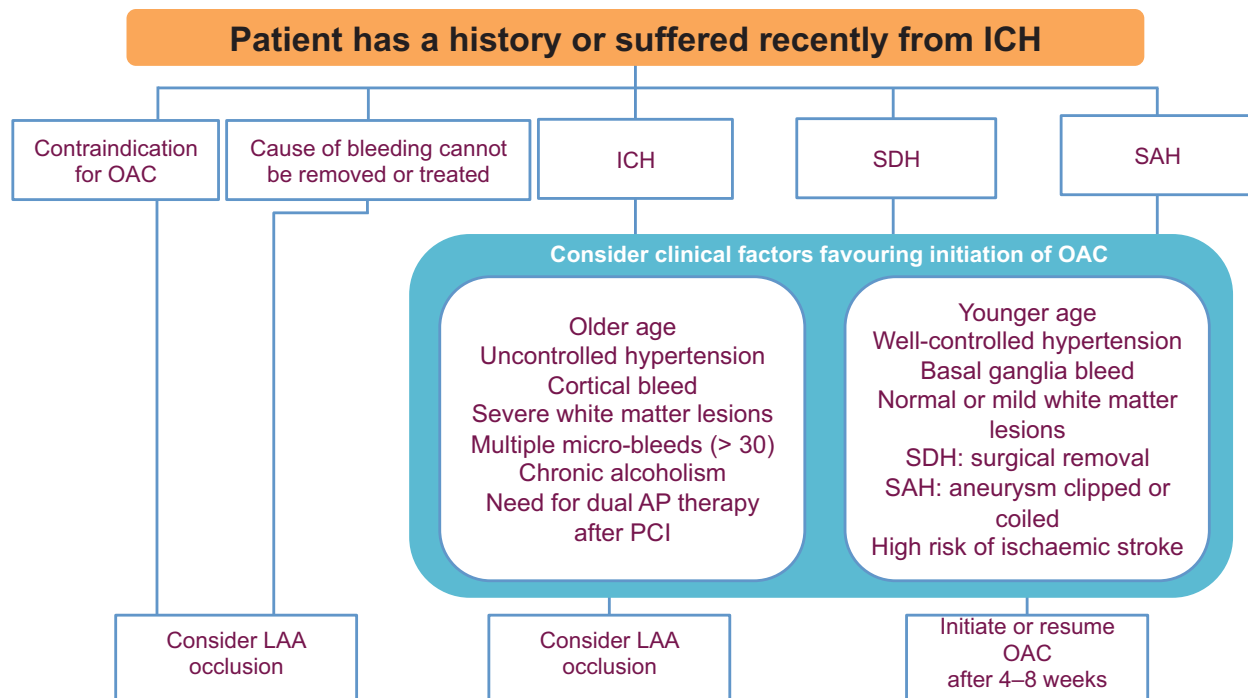
intracranial haemorrhage. In contrast to the patients included in the overall trials, patients with a prior TIA or ischaemic stroke were comparable in terms of risk factors and concomitant diseases at baseline. In 20,500 such patients, the rate of stroke (a composite of ischaemic and haemorrhagic stroke) and systemic embolism was significantly lower with NOACs than with warfarin; relative risk reduction: 13.7%; absolute risk reduction: 0.78%; and number needed to treat (NNT) to prevent one event: 127. The risk of any stroke was clearly lower: relative risk reduction: 13.1%; absolute risk reduction: 0.7%; and NNT: 142. The risk of haemorrhagic stroke was also lower: relative risk reduction: 50.0%; absolute risk reduction: 0.63%; and NNT: 157; as was the risk of intracranial haemorrhage, relative risk reduction: 46.1%; absolute risk reduction: 0.88%; and NNT: 113 over 1.8 to 2.8 years.<sup>122</sup> Therefore, NOACs are preferred over VKAs for secondary stroke prevention in AF patients. In addition, initiating VKAs in AF patients with stroke is potentially problematic, because the early reductions in the levels of protein C and protein S before the reduction in the levels of pro-thrombin may induce a transient hypercoagulable state.<sup>123</sup> This early hypercoagulable state does not occur with the NOACs.<sup>124</sup> Outcome trials with NOACs in secondary prevention after embolic stroke of undetermined source (ESUS) are ongoing, although the trial with rivaroxaban (NAVIGATE-ESUS) has been stopped early due to lack of benefit and a higher risk of bleeding with rivaroxaban than with aspirin.<sup>125</sup> Many patients with ESUS have undiagnosed underlying AF (which will become apparent with more prolonged and sophisticated monitoring),<sup>126</sup> and while current guidelines still recommend aspirin for ESUS patients, the optimal work-up and appropriate thromboprophylaxis for such patients if AF is not confirmed remains uncertain.<sup>127</sup>

#### Initiation of Anticoagulation after an Intracranial Haemorrhage

Patients with a history of intracranial haemorrhage were excluded from the randomized trials comparing the NOACs with warfarin. Resumption of anticoagulation after intracranial haemorrhage depends on the aetiology of the bleeding. When the cause or the source of the bleeding can be treated, such as hypertension, arteriovenous malformations, ruptured aneurysms or traumatic subdural haematoma, anticoagulation therapy can often be restarted 4 to 8 weeks after the initial event. In contrast, anticoagulation is contraindicated if the intracranial bleed was triggered by conditions associated with a high risk of recurrent bleeding, such as severe small vessel disease, > 30 microbleeds on MRI, cortical location of cerebral bleeds or spontaneous or minimally provoked subdural haematoma.<sup>121</sup> Although retrospective data from several registries suggest that anticoagulation therapy can safely be restarted in approximately 40% of patients with intracranial bleeding,<sup>128,129</sup> prospective studies are needed to confirm these findings. If anticoagulation cannot be restarted because of a high risk of recurrent intracranial bleeding, occlusion of the left atrial appendage should be considered<sup>121,130</sup> (► Fig. 2). Nonetheless, many patients are kept on aspirin post-left atrial appendage occlusion, and thus it remains uncertain if NOACs can safely be used in this setting, given the results of the AVERROES trial,<sup>131</sup> which revealed that apixaban was superior to aspirin for stroke prevention in AF patients considered unsuitable for VKA therapy and was associated with a similar rate of major bleeding.

#### Management of Concomitant AF and VTE

The NOACs are licensed for stroke prevention in AF and for the treatment of VTE. Both disorders are common, and



**Fig. 2** European Heart and Rhythm Association (EHRA) suggestions for initiation or resumption of oral anticoagulation in atrial fibrillation patients after an intracranial haemorrhage. Abbreviations: AF, atrial fibrillation; AP, anti-platelet; EHRA, European Heart and Rhythm Association; ICH, intracranial haemorrhage; LAA, left atrial appendage; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; SAH, sub-arachnoidal haemorrhage; SDH, sub-dural haematoma. Redrawn from Heidebuchel et al.<sup>162</sup>

patients may be diagnosed with AF and VTE concurrently.<sup>132</sup> Alternatively, patients receiving NOAC treatment for VTE may be subsequently diagnosed with AF, or patients treated with NOACs for AF may later be diagnosed with VTE. The overall approach to the management of each of these three scenarios is described below and summarized in ►Table 15.

### Concurrent Diagnosis of AF and VTE

It is not uncommon for patients with newly diagnosed VTE to have concomitant AF that was previously unrecognized or untreated. Anticoagulation treatment in such patients should be geared to the VTE. This is because the risk of recurrent thrombosis in patients with newly diagnosed VTE is highest in the first month and progressively declines thereafter. In contrast, the day-to-day risk of stroke with AF is constant. Because the risk of recurrence in VTE is front-loaded, treatment with apixaban or rivaroxaban starts with a higher dose—10 mg twice daily for 7 days or 15 mg twice daily for 21 days, respectively; the doses are then lowered to 5 mg twice daily and 20 mg once daily, respectively, thereafter. If dabigatran or edoxaban is selected, a minimum 5-day course of LMWH is required before starting the NOAC.<sup>133</sup>

Provided that the bleeding risk is not excessive, life-long anticoagulation is indicated for most patients with unprovoked VTE, or with risk factors for stroke.<sup>86,134</sup> A 3-month course of NOAC therapy may be sufficient for patients whose VTE was provoked by major transient risk factors, such as surgery or trauma, and with no risk factors for stroke,<sup>86</sup> such as those with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 0 in males or 1 in females. In most other cases, life-long treatment is warranted.

Guidelines suggest that patients with VTE in the setting of active cancer should be treated with a LMWH at least for the first 6 months.<sup>86</sup> This is reasonable for patients receiving systemic combination chemotherapy even though there is limited evidence that such treatment reduces the risk of stroke in AF patients. Once chemotherapy is completed, patients can be switched to a NOAC. Recent evidence from the Hokusai VTE-Cancer study demonstrated that the same dose of edoxaban approved for stroke prevention in AF (60 mg/day) is now a viable alternative to dalteparin and likely to other LMWH preparations in selected patients with active cancer.<sup>135</sup>

### AF in Patients Treated for VTE

Patients receiving NOACs for the treatment of VTE may subsequently be diagnosed with AF. The VTE treatment doses of NOACs after the first weeks are the same as those used for stroke prevention in AF, so no change in dosing is required. An exception is patients receiving lower doses of apixaban or rivaroxaban (2.5 mg twice daily and 10 mg once daily, respectively) for extended VTE treatment to prevent recurrence. Such patients should have their dose increased, except for patients treated with apixaban with at least 2 of the 3 dose reduction criteria (i.e., age 80 years or older, weight 60 kg or less and serum creatinine over 133 µmol/L [1.5 mg/mL]), who should remain on the lower-dose apixaban regimen.

### VTE in Patients Treated for AF

This is the most uncommon of the three scenarios. Potential triggers for VTE despite NOAC treatment include inadequate dosing, poor compliance, intake of concomitant medications

**Table 15** Management of concurrent atrial fibrillation and venous thromboembolism

Scenario	Management	Comments
Concurrent AF and VTE	Treat as for VTE	After initial treatment with higher dose apixaban or rivaroxaban or with LMWH bridging to dabigatran or edoxaban, dose NOACs according to AF dosing recommendations
VTE with newly diagnosed AF	Treat as for AF	If receiving low-dose apixaban or rivaroxaban (2.5 mg twice daily or 10 mg once daily, respectively) for extended VTE treatment, increase dose according to AF dosing recommendation. Dabigatran or edoxaban dosing for VTE is similar to that for AF so no change in dosing is required
AF with newly diagnosed VTE	If non-compliant or inappropriately receiving the lower-dose NOAC regimen, treat as for VTE. If compliant, consider a course of LMWH and then restart NOAC	Measure NOAC drug level to assess compliance. Evaluate for potential drug–drug interactions that may reduce NOAC exposure and if present consider changing medications or switching to a vitamin K antagonist. Exclude hyper-coagulable states such as cancer or anti-phospholipid syndrome as drivers of breakthrough thrombosis

Abbreviations: AF, atrial fibrillation; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.

that decrease drug exposure (such as potent P-gp and/or CYP3A4 inhibitors) and prothrombotic disorders such as cancer or the anti-phospholipid syndrome. Patients inappropriately receiving a lower-dose NOAC regimen can be treated as for VTE, and transitioned to the full-dose regimen. Measurement of NOAC levels may help identify poor compliance, while review of the medication list may identify drugs that could reduce NOAC exposure. Patients taking a multitude of such drugs may do better on monitored treatment with a VKA instead of a NOAC. If all of these possibilities are ruled out and there is no evidence of cancer, anti-phospholipid syndrome or other hypercoagulable conditions, it is reasonable to treat the VTE with LMWH for several weeks and then transition the patient back to a NOAC or, if there is a concern regarding adherence, to a VKA, so that the anticoagulant effect can be monitored.

### NOACs for VTE and AF in Cancer Patients

The properties of the NOACs, in particular their low propensity for drug–drug interactions and their proven efficacy and safety for VTE treatment and for stroke reduction in AF patients, render them as a viable alternative to LMWH or VKAs for VTE treatment or stroke prevention in patients with cancer. However, direct evidence from clinical trials in this setting is limited, and caution should be exercised for patients requiring chemotherapeutic agents interacting with P-gp and CYP3A4,<sup>136,137</sup> although no clear contraindication currently exists for any of these drugs.

#### VTE Prevention

No clinical trials have assessed the NOACs for VTE prevention in patients undergoing cancer surgery. Only one NOAC, betrixaban, was recently approved in the United States for VTE prevention in acutely ill medical patients, but detailed information on the cancer patients included in the trial is not

yet available.<sup>28</sup> A small phase II dose-finding study compared three doses of apixaban with placebo in outpatients receiving chemotherapy for advanced or metastatic cancer reported a low rate of bleeding with an apixaban dose of 2.5 mg twice daily.<sup>138</sup> This dose of apixaban is being compared with placebo in the AVERT study, which will include 500 cancer patients at risk for VTE (NCT02048865). In the similarly designed CASSINI study (NCT02555878), 800 cancer patients at risk for VTE will be randomized to rivaroxaban (10 mg once daily) or placebo.<sup>139</sup> The results of both studies are expected to be reported later this year.

#### VTE Treatment

The pivotal clinical trials comparing the NOACs with conventional anticoagulation, consisting of a LMWH overlapping with a VKA, for the treatment of VTE enrolled a variable proportion of patients with active cancer (~5%) or history of cancer. Although subgroup analyses and meta-analyses suggest a favourable risk–benefit profile of the NOACs, the comparator was a VKA and not LMWH—the currently recommended treatment for patients with cancer-associated VTE.<sup>116,140–145</sup> The Hokusai VTE-Cancer and Select-D trials compared edoxaban and rivaroxaban, respectively, with dalteparin for the treatment of cancer-associated VTE.<sup>146</sup> In the Hokusai VTE-Cancer study, edoxaban was non-inferior to dalteparin for the primary study outcome, a composite of first recurrent VTE or major bleeding.<sup>135</sup> VTE was reduced by edoxaban, but major bleeding occurred more frequently. However, the excess bleeding was confined to patients with gastrointestinal cancer.<sup>135</sup> Similar results were reported with rivaroxaban in the smaller Select-D pilot study. Likewise, in observational studies with rivaroxaban, its efficacy in patients with cancer appears to be similar to that in non-cancer patients, but there appears to be more bleeding.<sup>147</sup> Additional phase III trials with apixaban and rivaroxaban are underway, but the results of these studies

support the use of NOACs in place of LMWH selected patients with active cancer.

### Atrial Fibrillation

Patients with cancer were enrolled in the phase III AF trials that compared NOACs with warfarin, but little information is available for this subpopulation. In a subgroup analysis of the ARISTOTLE study, in which 6.8% of patients had cancer, the safety and efficacy of apixaban were preserved in patients with cancer compared with those without cancer, and the net clinical benefit was greater in patients with active cancer than in those without cancer.<sup>148</sup> Of note, only 157 of a total of 18,183 patients had active cancer or had received treatment for cancer within the past year. In a retrospective, single-centre cohort study that included 163 AF patients with active cancer treated with rivaroxaban, the cumulative incidence of ischaemic stroke and major bleeding was low, while the incidence of death was high, suggesting the inclusion of a population with active disease.<sup>149</sup> In a population-based claims database analysis, the risk of thromboembolic and bleeding complications in AF patients treated with NOACs

was similar in patients with and without cancer.<sup>150</sup> Finally, in a sub-group analysis of the ENGAGE AF-TIMI 48 study, cancer patients had higher rates of major bleeding than patients without cancer, and edoxaban was as effective as warfarin for the prevention of stroke, with a similar risk of major haemorrhages.<sup>151</sup> These results are exploratory and await validation.

### NOACs for Thromboprophylaxis in Medically Ill Patients

Patients hospitalized for acute medical illness are at risk for VTE, both during their hospital stay and for up to 3 months after discharge.<sup>152</sup> Evidence-based guidelines recommend that anticoagulant thromboprophylaxis be given to hospitalized medical patients at increased risk of VTE, and that prophylaxis should be continued for 6 to 21 days until the patient is fully mobile or is discharged from the hospital, whichever occurs first.<sup>153,154</sup> Current guidelines suggest against the routine use of extended thromboprophylaxis beyond the acute hospital stay.<sup>153,154</sup> This recommendation is based on the results of the EXCLAIM, ADOPT and MAGELLAN studies<sup>155,156</sup> (►Table 16),

**Table 16** Study design and results of randomized trials of NOACs for extended thromboprophylaxis in medical patients

	ADOPT	MAGELLAN	APEX	MARINER
Drug	Apixaban	Rivaroxaban	Betrixaban	Rivaroxaban
Regimen	2.5 mg twice daily	10 mg once daily	80 mg once daily	10 mg once daily
Reduced dose in selected patients	No	No	Yes <sup>a</sup>	Yes <sup>b</sup>
Timing of randomization	In hospital	In hospital	In hospital	At hospital discharge
D-dimer for patient eligibility	No	No	Yes	Yes
Treatment duration	30 d	35 ± 4 d	35–42 d	45 d
Comparator	Enoxaparin for at least 6 d	Enoxaparin for 10 ± 4 d	Enoxaparin for 6–14 d	Placebo
Double-blind design	Yes	Yes	Yes	Yes
Primary efficacy outcome	Asymptomatic proximal DVT and symptomatic VTE through day 30  Apixaban 2.7% Enoxaparin/placebo 3.10%	Asymptomatic proximal DVT and symptomatic VTE at days 10 and 35  Rivaroxaban 4.4% through day 35 Enoxaparin/placebo 5.7% through Day 35	Asymptomatic proximal DVT and symptomatic VTE through day 35  Betrixaban 6.9% Enoxaparin 8.5%	Symptomatic VTE through day 45  Rivaroxaban 0.83% Placebo 1.10%
Principal safety outcome	Bleeding  Apixaban 0.5% major 2.7% CRNM Enoxaparin/placebo 0.2% major 2.1% CRNM	Major or CRNM bleeding  Rivaroxaban 4.1% on day 35 Enoxaparin/placebo 1.7% on day 35	Major bleeding  Betrixaban 0.7% Enoxaparin 0.6%	Major bleeding  Rivaroxaban 0.28% Placebo 0.15%
Sample size	6,758	8,101	7,513	12,000

Abbreviations: CrCl, creatinine clearance; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; P-gp, P glycoprotein; VTE, venous thromboembolism.

Note: Table adapted from Raskob et al.<sup>165</sup>

<sup>a</sup>Betrixaban 2 doses of 80 mg given on day 1. Patients with CrCl 15 and < 30 mL/min, or if taking strong P-gp inhibitor drugs, receive one dose of 80 mg on day 1 and 40 mg once daily thereafter.

<sup>b</sup>Rivaroxaban 7.5 mg if CrCl is between 30 and < 50 mL/min.

which did not show a favourable benefit–risk profile for extended thromboprophylaxis with enoxaparin, apixaban or rivaroxaban, respectively, in the broad population of medical patients.

Advances in VTE risk assessment in medical patients<sup>152</sup> and the results of the APEX trial<sup>28</sup> (►Table 16) are shifting the current paradigm and might prompt a change in the guidelines. Using contemporary risk assessment models such as the IMPROVE or IMPROVEDD scores, we can now identify medically ill patients at high risk for VTE who can be targeted for extended thromboprophylaxis.<sup>152,157</sup> Using this approach, the APEX trial<sup>28</sup> compared betrixaban, started in hospital and continued for 35 to 45 days, with enoxaparin for 6 to 14 days, in 7,513 patients hospitalized for acute medical illness. Patients were eligible if they were 40 years of age or older and were hospitalized for specific medical illnesses, which included heart failure, respiratory failure, infectious disease, rheumatic disease or ischaemic stroke, and if they had specific risk factors for VTE, including age  $\geq 75$  years, age 60 to 74 years with a plasma D-dimer  $\geq 2$  times the upper limit of normal or age 40 to 59 years with a similarly elevated plasma D-dimer and a previous history of VTE or cancer. The main results are given in ►Table 16. Importantly, compared with enoxaparin, betrixaban reduced symptomatic VTE at 45 days from 1.5 to 0.9% (relative risk reduction: 36%,  $p = 0.04$ , NNT: 167) and all-cause stroke from 0.97 to 0.54% (relative risk reduction: 44%,  $p = 0.032$ , NNT: 233)<sup>28,158</sup> without increasing the risk of major bleeding. These findings prompted the licensing of betrixaban for extended thromboprophylaxis in medically ill patients by the FDA, but not, currently, by the European Medicinal Agency.

The results of the MARINER trial (►Table 16) render it unclear whether there is a net clinical benefit in extending thromboprophylaxis for 45 days after hospital discharge. Despite selection of apparently high-risk patients, the event rate in the placebo group was only 1.1%. Although major bleeding rates were low, the rate of out-of-hospital VTE is likely too low to justify routine extension of thromboprophylaxis.<sup>159</sup>

## Conclusion

The NOACs are replacing VKAs for many indications because they are at least as effective, more convenient to administer and associated with less intracranial bleeding. With the uptake of the NOACs rapidly increasing, it is important to use them safely and effectively.

The safety of the NOACs is likely to be enhanced with the availability of specific reversal agents. Idarucizumab is widely available for dabigatran reversal, and a reversal agent for the oral FXa inhibitors may soon be licensed. Whether 4FPCC is effective in this setting is uncertain. When andexanet alfa is approved worldwide for reversal of oral FXa inhibitors, studies to establish its effectiveness in the urgent surgical setting will be needed. Because andexanet also reverses heparin, its use prior to cardiac or vascular surgery may be problematic. Therefore, studies with 4FPCC or 3FPCC in this setting are warranted.

Emerging data support the use of NOACs for VTE treatment and stroke prevention in patients with cancer, although more data are needed to guide optimal care of this wide spectrum of clinically challenging patients. Because of the reduced risk of intracranial bleeding, the NOACs are preferred over VKAs for the treatment of selected patients with intracranial bleeding. However, identifying patients who can be safely started on NOACs after an intracranial bleed is complicated. Consultation with experienced neurologists is essential to facilitate such decisions.

There is some evidence of the benefit for extended thromboprophylaxis with betrixaban in high-risk medically ill patients. Ongoing studies, one of which is already completed, in cancer patients at high-risk for VTE are investigating the benefit–risk profile of primary thromboprophylaxis with NOACs relative to placebo. Therefore, the role of the NOACs for VTE prevention may be expanding.

In summary, the NOACs streamline prevention and treatment of thrombosis. Attention to renal function and concomitant medications is required to ensure that NOACs are appropriate and, if so, that the right dose is chosen. Given their short half-lives, adherence is pivotal to the translation of trial results into clinical practice. As the indications expand, widespread availability of tests to measure NOAC levels and agents to reverse their anticoagulant effects will become increasingly important. Therefore, there still is much to learn in the era of the NOACs, and continuing clinical research with these agents is warranted. In the meantime, development efforts on the next generation of anticoagulants are well underway, and these new agents will have to improve on the efficacy and safety profile of the current NOACs.<sup>160</sup>

## Conflict of Interest

The authors declare the following potential conflicts of interest:

Raffaele De Caterina declares fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, MSD and Portola.

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