

# New oral anticoagulants: a practical guide for physicians

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New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Unlike VKAs, these anticoagulants do not require routine INR monitoring and possess favorable pharmacological properties. The lack of an effective antidote, their cost, or reservations in patients with kidney disease may explain their slow rate of expansion. Safe and effective use of these new drugs will depend on clinical experience amongst the medical community. This review discusses the current NOACs, providing practical and easy-to-use algorithms for application in the clinical routine.

**Keywords** Atrial fibrillation • New oral anticoagulants • Stroke

## Introduction

Vitamin K antagonists (VKAs) have been the main stone for the antithrombotic prevention in atrial fibrillation (AF) for >60 years. Despite its unquestionable impact to prevent strokes, medical community have to deal with significant limitations, such as common drug or food interactions, and the necessity of regular monitoring to adjust doses, *inter alia*. In the last 5 years, oral anticoagulant therapy is now witnessing a revolution after the completion of large phase III clinical trials on the commonly termed the new oral anticoagulants (NOACs). Advantages of these new agents including the uses of fixed-dosing with no need for monitoring, few interactions, and a wider therapeutic window counteract with their current drawbacks. The lack of an effective antidote, their cost, or reservations in patients with kidney disease may explain their slow rate of expansion.

After the inevitable enthusiasm, it is the medical community responsibility to ensure the current appropriate use of NOACs that very much depends on the experience, and exhaustive knowledge of their indications and particularities in specific clinical scenarios.

This review discusses the new anticoagulants such as dabigatran, edoxaban, rivaroxaban, and apixaban, and provides practical and easy-to-use algorithms for application in the clinical routine specially focused on AF prophylaxis.

## New oral anticoagulants

Two classes of NOACs are currently available, the oral direct thrombin inhibitors (DTIs; e.g. dabigatran) and oral direct factor Xa

inhibitors (e.g. rivaroxaban, apixaban, and edoxaban). Unlike VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in coagulation.

Careful attention to patients' characteristics will ensure a correct prescription of antithrombotic therapies for patients with AF (Figure 1).

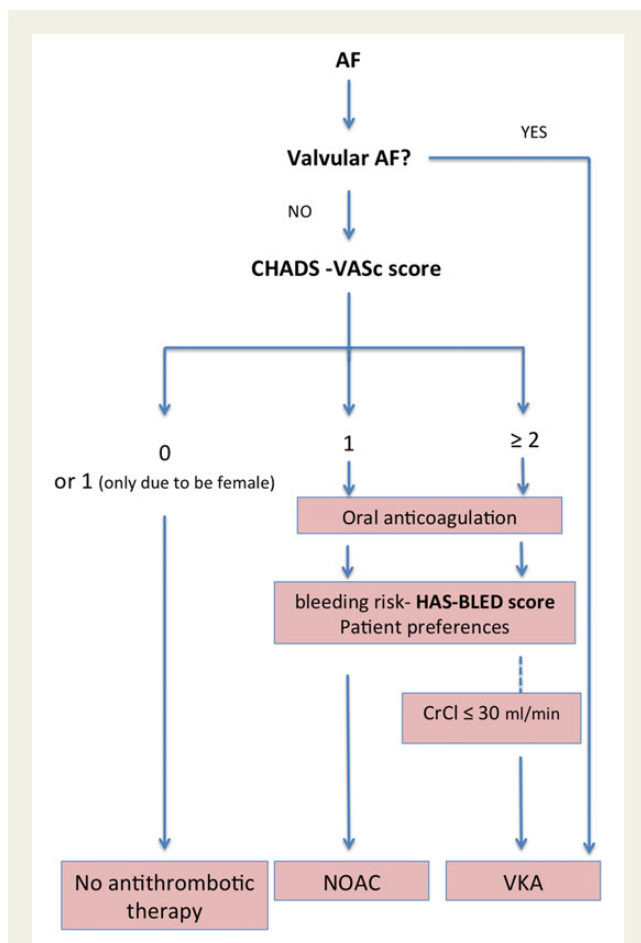
Recent data from seven European countries show a much better adherence to evidence and recommendations for oral anticoagulation.<sup>1</sup> Interestingly, NOACs were given to younger patients and only to 6% of the study populations, reflecting a tendency to prescribe these new therapies prudently at first and their inherent reimbursement limitations, respectively.

Figures 2–4 show recommended practical algorithms to ensure correct indications, interactions, and therapeutic dosing for each NOAC. At the moment of publication of this review, rivaroxaban, dabigatran, and apixaban are approved for antithrombotic prevention in AF by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).<sup>2–4</sup> Edoxaban has been recently approved by the FDA but not yet by the EMA. All three NOACs may be a reasonable option to VKAs for elective cardioversion.<sup>5–7</sup>

Recently, rivaroxaban, dabigatran, and apixaban have been approved for the treatment of venous thromboembolism (VTE), after showing non-inferiority in terms of efficacy in phase III clinical trials compared with the standard heparin/VKA regimen.<sup>8–15</sup> Slight differences in dose regimens are recommended when NOACs are indicated for AF prophylaxis or VTE treatment.

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**Figure 1** Choice of anticoagulant treatment. Adapted from ESC guidelines with permission.<sup>37</sup> AF, atrial fibrillation; CrCl, creatinine clearance; VKAs, vitamin K antagonists; NOAC, new oral anticoagulants.

## Dabigatran

Dabigatran etexilate was the first NOACs studied and FDA approved, based on the results of the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) trial.<sup>2</sup> Dabigatran is a highly specific and competitive direct thrombin inhibitor, which is orally administered as an inactive drug and after complete esterase-mediated conversion to its active form, reaches peak plasma levels within 2–3 h.<sup>16</sup> It has a rapid onset of action (1–2 h), a short half-life (12–17 h), and has an 80% renal excretion.

In contrast to VKAs, dabigatran has no major drug–food interactions and few drug–drug interactions. However, concurrent administration with P-glycoprotein inhibitors or P-glycoprotein inducers is contraindicated (Figure 2).<sup>17</sup> Although concomitant administration of dabigatran and pantoprazole may reduce the anticoagulant effect, dose adjustment is not considered necessary.<sup>16,18</sup>

The usual dose for dabigatran is 150 mg twice daily (BID), which has been approved by the FDA and the EMA. A lower dose of 110 mg BID, only approved by the EMA, is recommended for patients over age 80 or at high risk of bleeding (Figure 2). The FDA, but not the EMA, approved 75 mg BID for patients with creatinine clearance

(CrCl) of 15–30 mL/min based on pharmacokinetic models, but that dose has not been studied in the pivotal study of dabigatran.

## RE-LY and RELY-ABLE

The RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) phase III trial was a prospective, randomized, open-label, phase III trial comparing two blinded doses of dabigatran etexilate (110 or 150 mg BID) with warfarin in 18 113 patients with AF and at least one additional risk factor (a mean CHADS score of 2.1).<sup>2</sup> Patients with severely impaired renal function (CrCl <30 mL/min), active liver disease, stroke within 14 days, or at a high risk of bleeding were excluded.

For the primary efficacy endpoint of stroke and systemic embolism, dabigatran 150 mg BID was superior to warfarin with no significant differences in major bleedings. Gastrointestinal (GI) bleeding was more frequent with dabigatran 150 mg BD. Dabigatran 110 mg BD was non-inferior to warfarin for the primary endpoint, with a reduction of 20% in major bleedings. In the warfarin group, international normalized ratio (INR) was within the therapeutic range 64% of the study period beyond the first week.

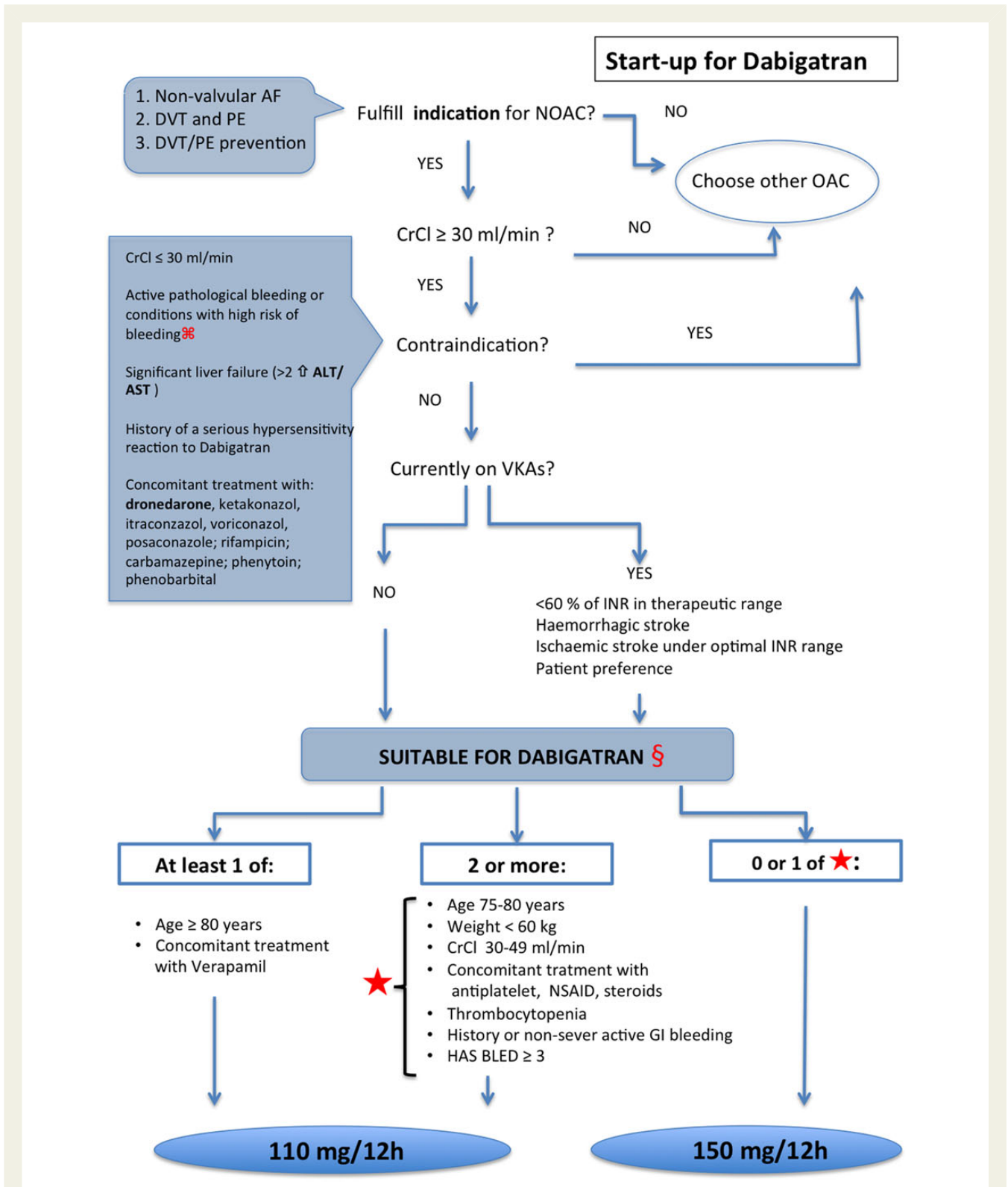
A *post hoc* analysis of 1989 electrical cardioversions in 1270 patients did not show significant differences in the rate of stroke within 30 days after the procedure between warfarin and dabigatran 110 or 150. About 25% of the patients underwent a transoesophageal study before cardioversion. There was no significant difference in the incidence rate of left atrial thrombus (1.1% for warfarin, 1.2% for dabigatran 150 mg BD, and 1.8% for 110 mg BD).<sup>5</sup>

The subsequent Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study provided additional information on the long-term effects of the two doses of dabigatran in patients completing RE-LY by extending the follow-up of patients on dabigatran from a mean of 2 years at the end of RE-LY by an additional 2.3 years.<sup>19</sup> No patients on warfarin were enrolled in this study. RELY-ABLE confirmed the results reported in RE-LY. Moreover, there were no significant differences in stroke or mortality between dabigatran 110 and 150 mg BD, but a higher rate of major bleeding was observed with the higher dose of dabigatran.

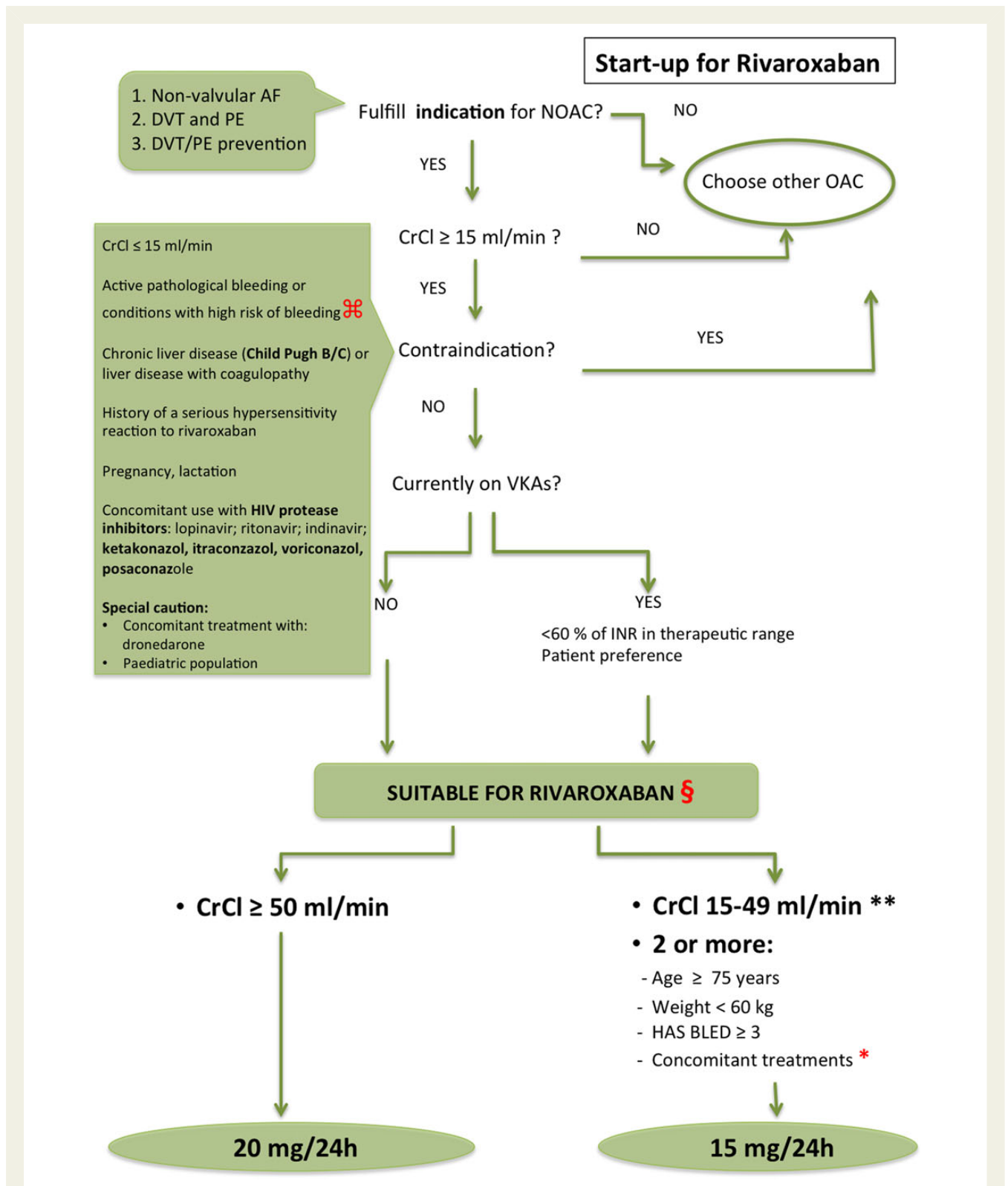
Recently, the safety profile of dabigatran (150 and 75 mg BD) in real US clinical practice has been reported in an elderly Medicare cohort with non-valvular AF.<sup>20</sup> Compared with warfarin, dabigatran was associated with a reduced risk of ischaemic stroke, intracranial haemorrhage and mortality, but with an increased risk of major GI bleeding. These results were stronger in the subgroup treated with dabigatran 150 mg BD. Around 16% of patients received dabigatran 75 mg BD and among these, none of the study outcomes were statistically significantly different from warfarin except for a lower risk of intracranial haemorrhage with dabigatran. Unfortunately, known severe renal impairment was only present in up to 7% of the subgroup of dabigatran 75 mg BD and results must be interpreted carefully.

## Rivaroxaban

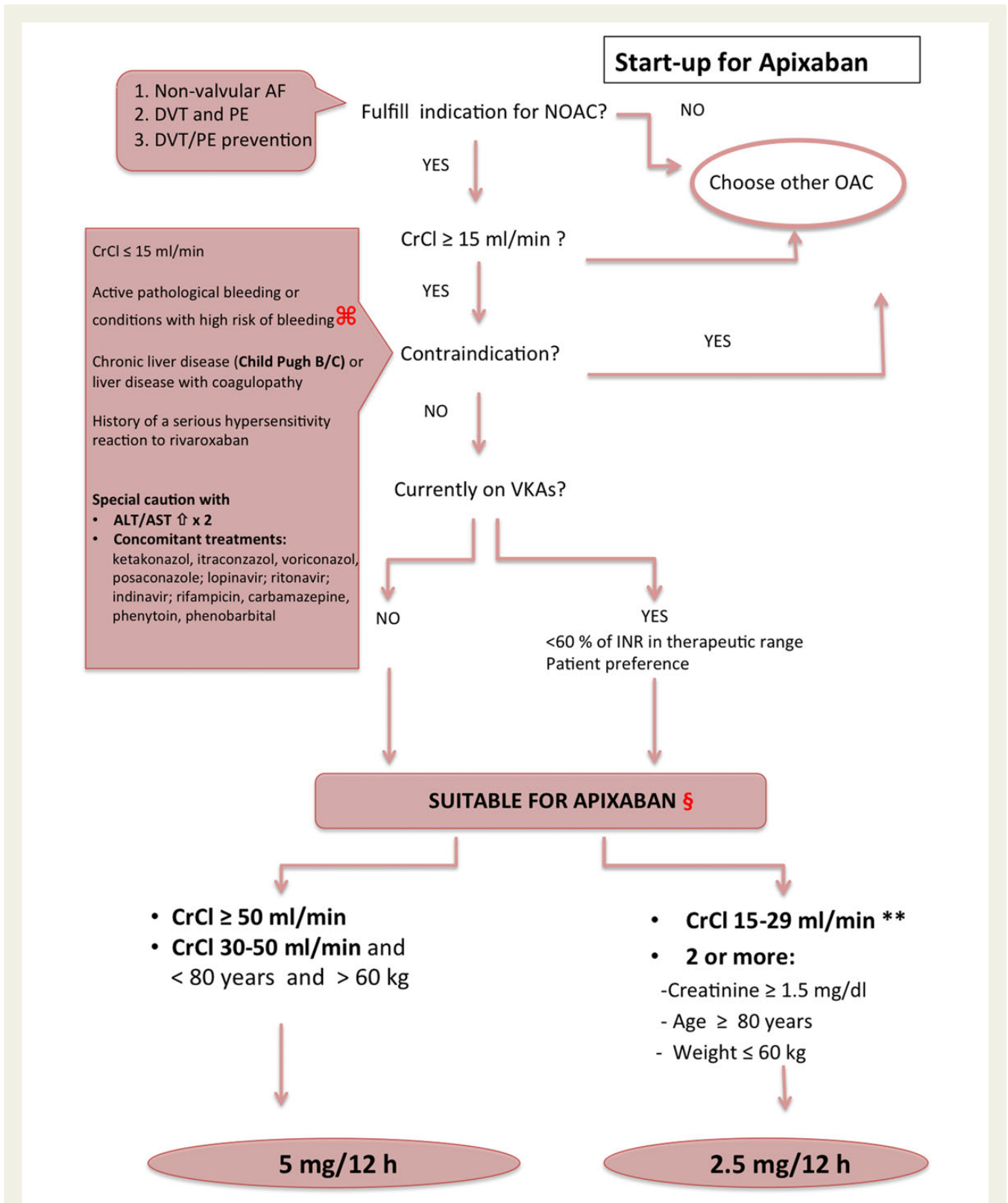
Rivaroxaban is a competitive and dose-dependent direct inhibitor of factor Xa and the second NOAC approved by the FDA and EMA based on the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for



**Figure 2** Start-up for dabigatran. ☞, active or recent gastrointestinal ulceration, presence of malignancy with high risk of bleeding, brain trauma, or recent brain surgery, spinal or ophthalmic, recent intracranial bleeding, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or intraspinal vascular anomalies or intracerebral higher. §, dose regimens for acute VTE: 150 mg BID; for VTE prevention after knee or hip replacement surgery (14 or 30 days, respectively): 110 mg (initial dose) then 220 mg daily. DVT, deep venous thrombosis; PE, pulmonary embolism; CrCl, creatinine clearance (preferably measured by the Cockcroft method); VKAs, vitamin K antagonists; INR, international normalized ratio; VTE, venous thromboembolism; BID, twice daily.



**Figure 3** Start-up for rivaroxaban. ☞, active or recent gastrointestinal ulceration, presence of malignancy with high risk of bleeding, brain trauma or recent brain surgery, spinal or ophthalmic, recent intracranial bleeding, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or intraspinal vascular anomalies or intracerebral higher. \*\*, Patients with CrCl < 30 mL/min were excluded from ROCKET AF; \*, concomitant treatments: quinidine, fluconazole, cyclosporin, tacrolimus, clarithromycin, erythromycin, rifampicin, carbamazepine, phenytoin, and phenobarbital; §, dose regimens for acute VTE: 20 mg daily (15 mg twice daily for initial 21 days); for VTE prevention after knee or hip replacement surgery (14 or 30 days, respectively): 10 mg daily; CrCl, creatinine clearance (preferably measured by the Cockcroft method); VKAs, vitamin K antagonists; INR, international normalized ratio; VTE, venous thromboembolism.



**Figure 4** Start-up for apixaban. ☞ active or recent gastrointestinal ulceration, presence of malignancy with high risk of bleeding, brain trauma or recent brain surgery, spinal or ophthalmic, recent intracranial bleeding, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or intraspinal vascular anomalies, or intracerebral higher. §, dose regimens for acute VTE: 5 mg twice daily (10 mg twice daily for initial 7 days); for VTE prevention after knee or hip replacement surgery (14 or 30 days, respectively): 2.5 mg twice daily; \*\*, Patients with serum creatinine level of >2.5 mg per deciliter or calculated CrCl <25 ml per minute were excluded from ARISTOTLE; CrCl, creatinine clearance (preferably measured by the Cockcroft method); VKAs, vitamin K antagonists; INR, international normalized ratio.

**Table 1** Pharmacological properties of new oral anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban <sup>a</sup>
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Pro-drug	Yes	No	No	No
Bioavailability, %	6%	66% without food up to 100% with food	50%	62%
Half-life, h	12–17 h	5–9 h (young) 11–13 h (elderly)	12 h	9–11 h
Time to maximum plasma concentration	0.5–2	2–4 h	1–4 h	1–2 h
Renal excretion	80%	35%	25%	50%
Liver metabolism	No	Yes	Yes	Minimal
Gastrointestinal tolerability	Dyspepsia	No problem	No problem	No problem
Absorption with food	No effect	+39% more	No effect	6–22% more
Intake with food?	No	Mandatory	No	No official recommendation
Dosing	Twice daily	Once daily	Twice daily	Once daily

<sup>a</sup>No European Medicines Agency approved yet.

Prevention of Stroke and Embolism Trial in Atrial Fibrillation).<sup>3</sup> It is rapidly absorbed and reaches peak plasma concentration within 2–4 hours after oral administration. It has a half-life of 9–13 hours with 35% renal clearance<sup>21–26</sup> (Table 1). Approximately two-thirds of an administered dose of rivaroxaban are metabolized by the liver via cytochrome P450 enzymes (CYP3A4 and CYP2J2). Therefore, concomitant treatment with cytochrome P450 isoenzymes and P-glycoprotein inhibitors, such as itraconazole and voriconazole, is contraindicated due to an increased risk of bleeding (Figure 3). Since one-third of the drug is eliminated by the kidneys, rivaroxaban is contraindicated in patients with severe renal insufficiency.

It is administered 20 mg once daily with a large meal to increase bioavailability. A 15 mg dose is recommended for patients with mild renal impairment, high risk of bleeding, and/or potential drug–drug interactions (Figure 3)

## ROCKET AF

The ROCKET AF was a double-blinded study in which 14 264 patients with non-valvular AF and CHADS<sub>2</sub> scores  $\geq 2$  (mean 3.5) were randomly assigned to rivaroxaban 20 mg once daily or dose-adjusted warfarin; patients with CrCl of 30–49 mL/min received 15 mg of rivaroxaban. Those with CrCl of  $< 30$  mL/min, significant liver disease, any stroke within 14 days (or severe strokes within 3 months), HIV infection, concomitant treatments with non-steroidal anti-inflammatory drugs, inhibitors of cytochrome P450 3A4, inducers of cytochrome P450 3A4, or at a high risk of bleeding were excluded.

After a median follow-up of 1.93 years, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism; however, rivaroxaban failed to show superiority over warfarin in the intention-to-treat analysis ( $P = 0.12$ ). There were no differences in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. Gastrointestinal bleeding and transfusion requirements were greater with rivaroxaban. Total mortality was not significantly different between groups.

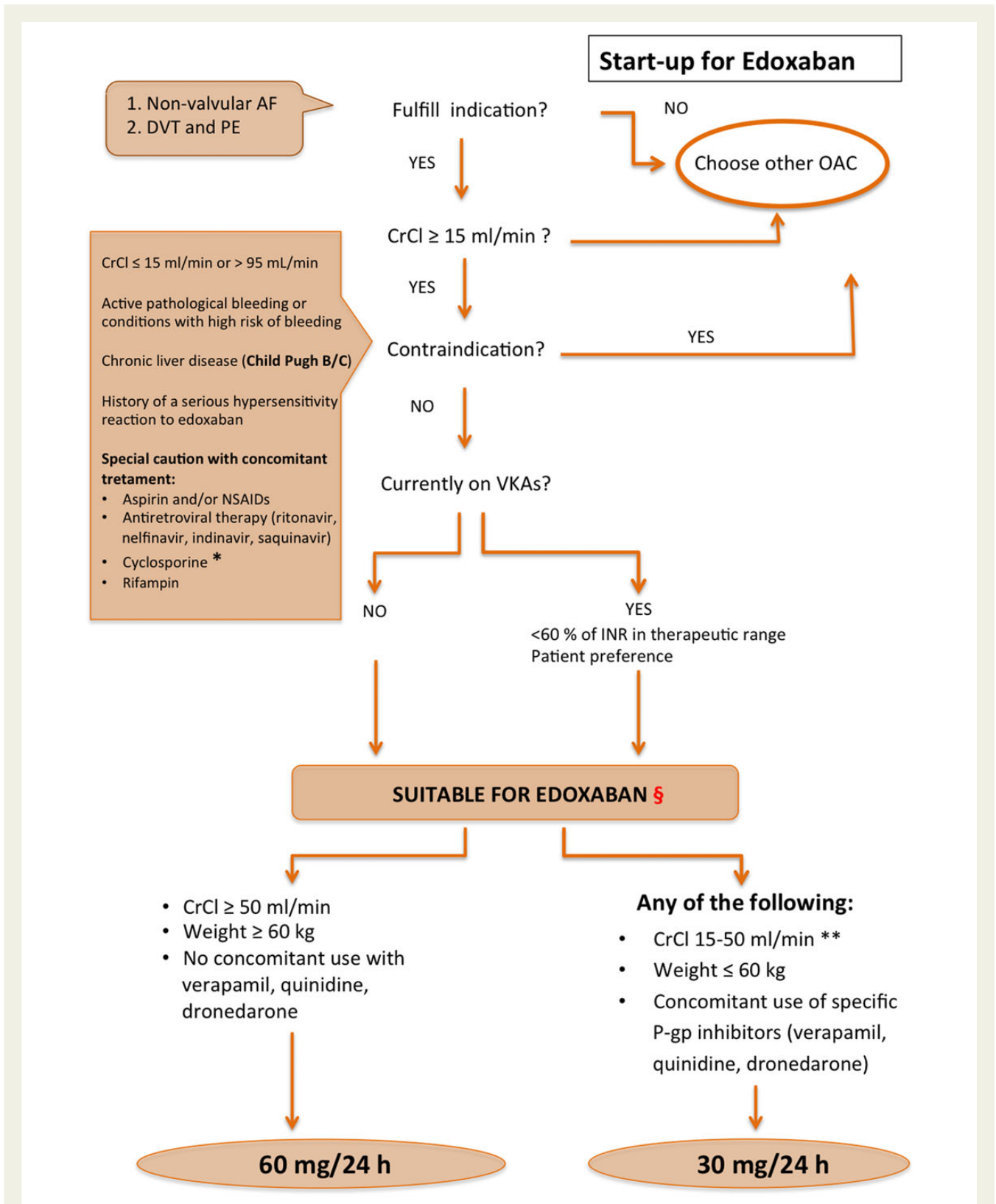
## Apixaban

Apixaban is a direct, reversible, competitive, and selective inhibitor of factor Xa and the last NOAC approved by the FDA and EMA for the prevention of stroke and embolism in non-valvular AF. It is well absorbed achieving peak plasma concentration in 1–4 h.<sup>27–29</sup> Current recommended dosing is 5 mg BID daily for patients with normal renal function and 2.5 mg BID for patients with two of the following characteristics: age  $> 80$  years, body weight  $< 60$  kg, and serum creatinine  $> 1.5$  mg/dL (Figure 4). It is predominantly metabolized by the liver and similar to rivaroxaban, apixaban is contraindicated in concomitant use with drugs capable of inducing or inhibiting CYP3A4.<sup>4</sup>

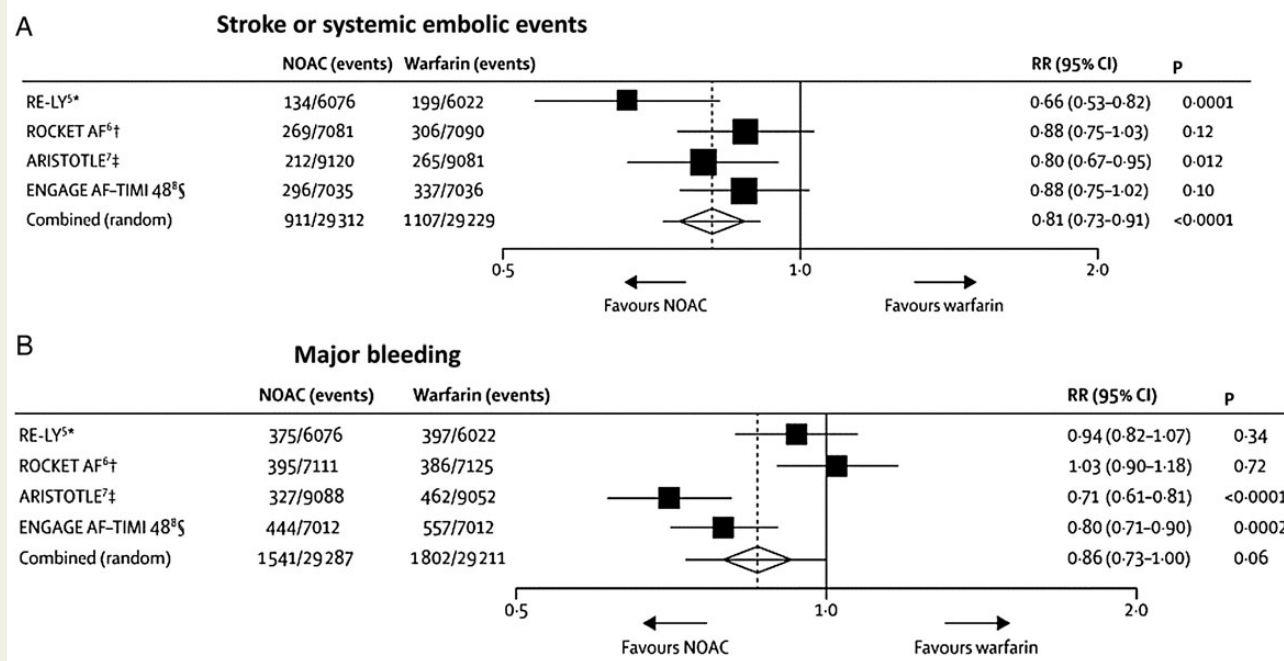
## ARISTOTLE and AVERROES

The Apixaban for Reduction In STroke and Other Thromboembolic Events in AF (ARISTOTLE) was a randomized, double-blinded, double-dummy, phase III trial comparing apixaban (5 mg BID) with dose-adjusted in 18 201 patients with non-valvular AF (a mean CHADS<sub>2</sub> score of 2.1).<sup>4</sup> Apixaban 2.5 mg BID was used among patients with two or more of the following conditions:  $> 80$  years of age, weight  $< 60$  kg, or a serum creatinine level  $> 1.5$  mg/dL. After a mean follow-up of 1.8 years, apixaban was significantly better than warfarin, with fewer primary outcomes (overall strokes—both ischaemic and haemorrhagic—and systemic emboli), but with no significant differences in rates of ischaemic strokes. Patients treated with apixaban had significantly fewer intracranial bleeds, but GI bleedings were similar between both groups. All-cause mortality was found to be significantly lower in the apixaban group.

Apixaban was also compared with aspirin alone in the AVERROES study, a double-blinded study of 5599 patients who were not suitable candidates for VKA treatment (mean CHADS<sub>2</sub> score of 2).<sup>30</sup> After a mean follow-up of 1.1 years, the study was prematurely stopped due to a clear benefit in favour of apixaban. The primary outcome of stroke or systemic embolism was significantly lower in the apixaban



**Figure 5** Start-up for edoxaban. §, history of intracranial, intraocular, spinal, retroperitoneal, or intraarticular bleeding; overt gastrointestinal bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 d; active infective endocarditis; uncontrolled hypertension (blood pressure N170/100 mm Hg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder. \*, This population was excluded in clinical trials; §, edoxaban is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant. Dose regimens for acute DVT and PE: 60 mg once daily or 30 mg once daily in patients with CrCL 15 to 50 mL/min, patients who weigh less than or equal to 60 kg, or patients who are taking certain concomitant P-gp inhibitor medications. \*\*, Patients with CrCL < 30 ml/min were excluded from ENGAGE AF-TIMI 48; CrCL, creatinine clearance (preferably measured by the Cockcroft method); VKAs, vitamin K antagonists; INR, international normalized ratio.



**Figure 6** (A) Stroke or systemic embolic events. (B) Major bleeding. Data are n/N, unless otherwise indicated. Heterogeneity:  $I^2 = 47\%$ ;  $P = 0.13$ . NOAC, new oral anticoagulant; RR, risk ratio. \*, dabigatran 150 mg twice daily; †, rivaroxaban 20 mg once daily; ‡, apixaban 5 mg twice daily; §, edoxaban 60 mg once daily. Reproduced from Ruff *et al.*<sup>36</sup> with permission.

group versus aspirin, whereas bleeding risk (major bleeding and intracranial bleeding) between two groups was similar.

Patients with severe renal impairment (serum creatinine  $>2.5$  mg/dL or CrCl  $<25$  mL/min) were excluded from the ARISTOTLE and AVERROES trials.<sup>4,30</sup> Additional exclusion criteria were stroke within the previous 7 days, and concomitant treatment with aspirin at a dose of  $>165$  mg a day or for both aspirin and clopidogrel.

## Edoxaban

Edoxaban is another reversible factor Xa inhibitor, recently approved by the FDA but not yet by the EMA. It is rapidly absorbed and reaches peak plasma concentration within 1–2 h. Up to 50% of edoxaban is eliminated by the kidneys. Since it is a substrate for P-glycoprotein, concomitant administration with quinidine, amiodarone, and verapamil will result in a significant increase of plasma levels of edoxaban.<sup>31–34</sup> Therefore, in patients under concomitant use of potent glycoprotein inhibitors (verapamil or quinidine), body weight  $<60$  kg, or moderate–severe renal impairment (CrCl 50 mL/min), edoxaban dose should be reduced by 50%.

## ENGAGE AF-TIMI

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was a three-group, randomized, double-blinded, double-dummy phase III trial, which compared the two dose regimens of edoxaban (30 and 60 mg once daily) with warfarin<sup>35</sup> in a total of 21 026 patients with non-valvular AF. For patients in

either group of edoxaban, the dose was halved in any of the following characteristics: CrCl of 30–50 mL/min, body weight of 60 kg or less, or concomitant use of verapamil or quinidine.

After a follow-up of 2.8 years, both regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism; however, the lower dose trended toward inferiority, with a hazard ratio of 1.13 vs. Warfarin, and was inferior to specifically prevent ischaemic stroke. Edoxaban was associated with lower, dose-related rates of bleeding, including major bleeding, intracranial bleeding, and life-threatening bleeding. An exception was GI bleeding, which occurred more frequently with high-dose edoxaban but less frequently with low-dose edoxaban compared with warfarin. Finally, the incidence rate of haemorrhagic stroke and the rate of death from cardiovascular causes were significantly lower with both edoxaban regimens.

Patients with severe renal dysfunction (CrCl  $<30$  mL/min), high risk of bleeding, use of dual antiplatelet, acute coronary syndromes or coronary revascularization, and strokes within 30 days were excluded.

## Comparison between new oral anticoagulants

For the time being, no direct head-to-head comparisons between NOACs have been made in randomized, controlled trials, and extrapolation from primary trial data is the best available strategy for medical prescription. However, differences in trial design, in the estimated risk for stroke in the study population, comparator uniformity,



**Table 2** Suggested use of NOACs according to patient characteristics

Patients characteristics	NOAC	Dose regimen
High risk of stroke (high CHADS-VASC score)	Dabigatran	150 mg BID
Previous stroke	Rivaroxaban	20 mg QD
High risk of bleeding or previous life-threatening bleedings	Dabigatran Apixaban	110 mg BID 5 mg BID
Dyspepsia	Rivaroxaban Apixaban	20 mg QD 5 mg BID
GI bleeding	Apixaban	5 mg BID
Medication compliance problems	Rivaroxaban	20 mg QD
Elderly ( $\geq 80$ years) and impaired renal function	Apixaban	2.5 mg BID

NOAC, new oral anticoagulants; GI, gastrointestinal; BID, twice daily.

and definitions of efficacy and safety endpoints make complex direct comparisons. The choice of one or another NOAC for a given patient is influenced by individual patient characteristics, including risk of stroke or VTE, risk of bleeding, and comorbidity such as the presence of impaired renal function.

Figure 6 shows the comparative efficacy of high-dose of NOACs and warfarin.<sup>36</sup> Comparative analysis of the four NOACs confirmed that NOACs significantly reduced the composite of stroke or systemic embolic events by 19% compared with warfarin, which very much depended on large reduction in haemorrhagic strokes. Data for all four NOACs showed that they were associated with a 14% non-significant reduction in major bleedings.<sup>36</sup>

Although there is insufficient evidence to recommend one NOAC over another, Table 2 summarizes general recommendations based on patient characteristics, drug compliance, and tolerability. For instance, dabigatran may produce dyspepsia, but this NOAC at 150 mg BID was the only agent to demonstrate a reduction in ischaemic stroke. All NOACs except apixaban were associated with more GI bleeding than warfarin. Both rivaroxaban and apixaban are less dependent on renal elimination than dabigatran. Rivaroxaban and edoxaban have the benefit of once-daily dosing, which may be attractive for those patients who are less compliant. Therefore, patients with a history of these specific features might lead the clinician to prescribe one particular NOAC. However, it is important to highlight that at present all NOACs are clinically indicated in non-valvular AF regardless the estimated risk of stroke or bleeding.

Finally, VKAs remain the first-line anticoagulant for patients with mechanical heart valves or rheumatic heart disease and for those with severe renal insufficiency, in whom NOACs are contraindicated. Although low doses of rivaroxaban and apixaban have been approved by the EMA and the FDA (and 75 mg dabigatran and 30 mg edoxaban just by the FDA) for CrCl between 15 and 30 mL, there are no outcome data in this vulnerable population and current ESC guidelines does not recommend their use in such patients.<sup>37</sup> According to patient preference, VKAs remain a reasonable option for those with well-controlled INR values.

**Table 3** Effect of NOAC in coagulation test and possible measures in case of bleedings

Drug	Dabigatran	Factor Xa inhibitors
Effect on coagulation tests	$\uparrow$ : dTT, ECT, $\uparrow$ aPTT or no change: PT (not recommended)	$\uparrow$ : Anti-factor Xa $\uparrow$ or no change: PT, aPTT No change: dTT, ECT
Reversal in emergency bleeding	Oral charcoal Haemodialysis PCC, aPCC Desmopressin Antifibrinolytic agents	PCC, aPCC Desmopressin Antifibrinolytic agents

PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; PCC, prothrombin complex concentrate.

## How to measure effect

A clinical advantage of NOACs is their predictable anticoagulant effect enabling the administration of fixed doses without the need of routine monitoring. However, the lack of a reliable method or a clear marker of anticoagulant activity makes ensuring compliance very difficult. In addition, estimation of anticoagulation level might be useful in particular scenarios such as during acute bleeding, or stroke or when patients need an urgent surgery.

Table 3 simplifies the expected coagulation results when receiving NOACs. When interpreting these results, it is essential to take into account when the last dose of NOAC was administered since its maximum effect will be reached at its maximal plasma concentration. Furthermore, the estimated elimination half-life will depend on patient characteristics, and particularly important, on renal function, especially for those NOAC with a high renal clearance.

Although quantitative tests for NOAC assessment exist, such as DTIs and FXa inhibitors, they are not commonly available in most hospitals. Nevertheless, other more common tests may assess qualitatively NOAC activity. For *dabigatran*, diluted thrombin time (dTT), activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT) can be useful; an aPTT level (i.e. 12–24 h after ingestion) of  $\geq 2$  the upper limit of normal or ECT  $\geq 3$  times elevated may be associated with a higher risk of bleeding.<sup>38,39</sup> A dTT with appropriate calibrators for dabigatran is also available (Hemoclot<sup>®</sup>) and that with the Hemoclot<sup>®</sup> > 200 ng/mL after 12 h of the last dose is associated with a higher risk of bleeding as well. Each *factor Xa inhibitor* (*rivaroxaban*, *apixaban*, and *edoxaban*) affects the PT and aPTT to a different extent, and any of these tests is ideal to assess anticoagulant effect. Activated partial thromboplastin time has a weak prolongation under these NOACs and suffers of variability of assays, and paradoxical response at low concentrations. On the other side, PT is prolonged in a concentration-dependent manner for factor Xa inhibitors; however, its effect depend on the assay and on the particular factor Xa inhibitor. It could be useful for rivaroxaban, although sensitivity depends very much on the PT reagents. In particular, Neoplastin Plus has a close correlation to plasma concentrations of

rivaroxaban. There are currently no much data available for edoxaban and apixaban.

Finally, plasma concentrations of factor Xa inhibitors can be estimated by the commercially available Anti-FXa 'chromogenic assays' with good interlaboratory precision. Unfortunately, practical data to associate a coagulation parameter or level with bleeding risk are not yet available.

## 'What if' scenarios

### Patient has a bleeding complication

For the time being, specific antidotes for NOACs are lacking and the strategies to reverse anticoagulant effect are limited. Although this is considered a major drawback for their use, a recent meta-analysis presenting data on the management and outcome of major bleeding events in five phase III trials (dabigatran vs. AVK) showed a better outcome in those receiving dabigatran, reflected as a significantly shorter stay in the intensive care unit and a trend towards lower adjusted all-cause mortality at 30 days.<sup>40</sup> Time is the best advantage of NOACs, in view of their relatively short elimination half-lives.

If a major bleeding complication occurs, standard supportive measurements must be started. These include mechanical compression, surgical haemostasis, fluid replacement, and additional haemodynamic support.

Haemodialysis can accelerate drug removal in those patients receiving dabigatran; however, its benefit in life-threatening bleeding has not been established. In contrast, dialysis is not effective for factor Xa inhibitors due to their high plasma binding and lower renal clearance. The administration of prothrombin complex concentrate (PCC) or activated prothrombin complex (aPCC) concentrates can be considered in life-threatening bleeding, despite the scarce evidence. Administration of PCC could start at a dose of 25 U/kg and can be repeated if clinically indicated. If available aPCC could be also considered, starting at 50 IE/kg

(maximum 200 IE/kg/day). Additionally, other pro-coagulants such as antifibrinolytics or desmopressin can also be considered, but again there is no clinical evidence on their effectiveness.

Finally, a monoclonal antibody Fab molecule directed against dabigatran and a specific recombinant protein (r-antidote) to reverse the anticoagulant effect of the factor Xa inhibitor are now being investigated and hold promise in treating bleeding in life-threatening situations.<sup>41–43</sup>

### Patient undergoes intervention

The most appropriate management should be individualized depending on the NOAC used, the type of surgery, the required anaesthetic regimen, and the patients' characteristics, particularly, on their renal function.

For patients undergoing minor interventions, NOACs can be continued around the time of the procedure, similar to VKA-treated patients. Some examples include skin cancer removal, joint injection, cataract removal, or tooth extraction in which an adequate local haemostasis is commonly possible. Intervention should not be performed at peak concentrations but 12 or 24 h after the last intake, depending on their specific regimen dosing (once or twice daily).

However, if substantial bleeding is expected, the patient should skip 1–2 days of the NOAC before the procedure and re-start the NOAC on the next day after the procedure. *Table 4* suggests a pre- and post-surgery approach depending on the type of surgery, the type of NOAC, and renal function. Treatment should be delayed for at least 24 h after surgery, given the rapid onset of action of these drugs.

### Patient need to switch between anticoagulant regimens

*Table 5* summarizes how to switch from different anticoagulant regimens. Individual precautions must be kept in mind, particularly in those patients with impaired renal function.

**Table 4** Pre- and postoperative management of patients taking NOACs

NOAC	Renal function	Minor surgery <sup>a</sup>		Major surgery <sup>b</sup>	
		Preoperative management	Postoperative management	Preoperative management	Postoperative management
Dabigatran	Normal or mildly impaired (CrCl >50 mL/min)	Stop 2 days before surgery (skip 2 doses)	Re-start 24 h after surgery	Stop 3 days before surgery (skip 4 doses)	Re-start 48 h after surgery
	Moderately impaired (CrCl 30–50 mL/min)	Stop 3 days before surgery (skip 4 doses)		Stop 4–5 days before surgery (skip 6–8 doses)	
Rivaroxaban	Normal, mild, or moderately impaired (CrCl >30 mL/min)	Stop 2 days before surgery (skip 1 dose)	Re-start 24 h after surgery	Stop 3 days before surgery (skip 2 doses)	Re-start 48 h after surgery
Apixaban (CrCl >30 mL/min)	Normal, mild, or moderately impaired	Stop 2 days before surgery (skip 1 dose)	Re-start 24 h after surgery	Stop 3 days before surgery (skip 4 doses)	Re-start 48 h after surgery

<sup>a</sup>Minor surgery: Endoscopy with biopsy; prostate or bladder biopsy; electrophysiological study or simple radiofrequency catheter ablation tachycardia; angiography; pacemaker or ICD implantation.

<sup>b</sup>Major surgery: Complex left-sided ablation (pulmonary vein isolation and ventricular tachycardia ablation); spinal or epidural anaesthesia; lumbar diagnostic puncture; thoracic surgery; abdominal surgery; major orthopaedic surgery; liver biopsy; transurethral prostate resection; kidney biopsy.

**Table 5** Recommendation on how to switch between different anticoagulant regimens

Switching	How?
VKA to NOAC	Once the INR is lower than 2.0
Intravenous unfractionated heparin (UFH) to NOAC	After 2 h of stopping UHF (longer in cases of renal impairment)
Low-molecular-weight heparin (LMWH) to NOAC	When the next dose of LMWH was revised
NOAC to VKA	Concomitant treatment until INR 2–3
NOAC to parenteral anticoagulant (UFH, LMWH)	When the next dose of NOAC was planned
One NOAC to another	When the next dose of NOAC was planned (longer in cases of renal impairment)

## Conclusion

New oral anticoagulants have shown to have a favourable balance between efficacy and safety compared with VKAs, and three are now available for the prevention of stroke in non-valvular AF. Advantages of NOACs include fewer interactions with medications and no interaction with food, rapid onset, fast clearance, and no need for laboratory monitoring. Individualized anticoagulant treatment should be based on patients' age, renal function, and concomitant treatments. The rate at which VKAs will be replaced by NOACs will depend on clinical experience, patients' tolerance to these drugs, novel data from further studies, reimbursement policies, and other market forces. Further research is underway to develop reliable and accessible measures to monitor the anticoagulant effects of the new agents, as well as antidotes with the ability to effectively reverse anticoagulation effect.

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