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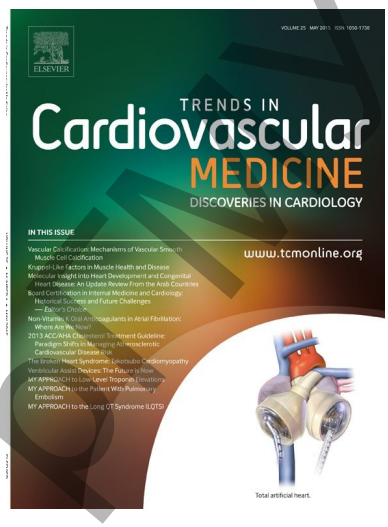

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INVITED REVIEW

Non-vitamin K Oral Anticoagulants in atrial fibrillation: where are we now

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Abstract

Atrial fibrillation (AF) confers increased risk of stroke and other thromboembolic events, and oral anticoagulation therefore is the essential part of AF management to reduce the risk of this complication. Until recently, the vitamin K antagonists (VKAs, e.g. warfarin) were the only oral anticoagulants available, acting by decreased synthesis of vitamin K-dependent coagulation factors (II, VI, IX, and X). The VKAs had many limitations: delayed onset and prolonged offset of action, variability of anticoagulant effect among patients, multiple food and drug interactions affecting pharmacological properties of warfarin, narrow therapeutic window, obligatory regular laboratory control, which all made warfarin 'inconvenient' both for patients and clinicians. The limitations of VKAs led to development of new class of drugs collectively defined as non-VKA oral anticoagulants (NOACs), which included direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). The NOACs avoid many of the VKA drawbacks. In this review we will focus on the current evidence justifying use of NOACs in non-valvular AF.

Key words: atrial fibrillation, non-vitamin K oral anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, warfarin

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, which confers an increased risk of stroke and other thromboembolic events. Oral anticoagulation therefore is the essential part of AF management to reduce the risk of these complications, irrespective of AF type (paroxysmal, persistent, or permanent).[1,2] The diagnosis of AF has improved dramatically during past years with various up to date arrhythmia screening technologies became available, allowing detection of asymptomatic and rare AF episodes in substantial proportion of patients, and appropriate stroke prophylaxis is also required in this group.[3,4]

Until recently, the vitamin K antagonists (VKAs, e.g. warfarin) were the only oral anticoagulants available, acting by decreased synthesis of vitamin K-dependent coagulation factors (II, VI, IX, and X; see Figure 1) by inhibition of VKORC1 (vitamin K epoxide reductase complex subunit 1), which is essential enzyme for vitamin K turnover in the human body.[5]
The VKAs have many limitations: delayed onset and prolonged offset of action, variability of anticoagulant effect among patients, multiple food and drug interactions affecting pharmacological properties of warfarin, narrow therapeutic window, obligatory regular laboratory control, broad targets of action (e.g. warfarin interferes with synthesis of other than coagulation factors vitamin K dependent proteins and eventually may lead to development of soft tissues calcification, osteoporosis, skin necrosis), which all make warfarin 'inconvenient' both for patients and clinicians. The variability of anticoagulant effect among patients results from genetic polymorphism of VKORC1 and several other genes. Regular laboratory monitoring is obligatory to maintain the INR within 2.0-3.0, and to ensure a high time in therapeutic range (TTR).[5]

The limitations of VKAs led to development of new class of drugs collectively defined as non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs[6]), which included direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) that avoid many of the VKA drawbacks.[7] In this review we will focus on the current evidence justifying use of NOACs for stroke prevention in non-valvular AF.

Decision making for stroke prevention versus bleeding, NOACs versus warfarin

Oral anticoagulation therapy in AF patients always requires balancing the risk of stroke and other thromboembolic complications on the one hand and risk of bleeding (especially major bleeding), on the other. Therefore precise estimation of stroke and bleeding risk is obligatory both before treatment initiation and during follow-up.[1,2] The risk of stroke and thromboembolic complications in AF patients depends largely on combination of various risk factors, which have been incorporated into various stroke risk assessment tools.

Many guidelines now recommend the CHA_2DS_2-VASc score[8] (Table 1), which is best in distinguishing patients with low risk (CHA_2DS_2-VASc score of 0 in males or 1 in females) who do not require any antithrombotic therapy given the negative net clinical benefit in such patients (i.e. reduction of stroke and systemic embolic events does not outweigh increase of bleeding events).[9-11] For other AF patients with ≥1 additional stroke risk factors (i.e. CHA_2DS_2-VASc score ≥ 1 in males or ≥2 in females) the net clinical benefit from oral anticoagulation is positive, showing that significant reduction of stroke rate can be achieved

balanced against a small increase of bleeding events, however, this has not been tested in randomized controlled trials.[9-11]

There are some differences between the European Society of Cardiology (ESC) and American College of Cardiology (ACC) /American Heart Association (AHA) /Heart Rhythm Society (HRS) guidelines for the management of AF. While according to ESC guidelines in AF patients with the CHA_2DS_2-VASc = 1 oral anticoagulation should be considered, ACC/AHA/HRS guidelines allow choice between no treatment, aspirin or oral anticoagulation.[1,2] Despite no one of these approaches have been tested in large randomised controlled trials, stroke rate can be as high as 1.1 per 100 person-years in this subset of patients.[12] Given the overlapping of the CHA_2DS_2-VASc and $CHADS_2$ scores because of incorporation of the common risk factors with the same weight of 1 into two scores, one patient with the CHA_2DS_2-VASc = 1 may also have $CHADS_2$ = 1, for which estimated stroke rate is even higher.[13,14] Thus, part of patients will be exposed to unnecessary risk of disabling or even fatal stroke that can otherwise be prevented with oral anticoagulation.

Among bleeding risk scores, the HAS-BLED score[15] (Table 1) is recommended to assess patients' one-year risk of haemorrhage given its simplicity for use in everyday practice and high performance in different subsets of patients, and, particularly, ability to predict intracranial haemorrhage (ICH) that is undoubtedly the most feared complication of oral anticoagulation therapy.[16]

Despite a range of limitations, warfarin is highly effective for stroke prevention in AF, reducing stroke by 64 % (95% confidence interval [CI] 49-74), both in primary (2.7% annual

absolute risk reduction) and secondary (8.4% annual absolute risk reduction) settings, as well as reducing all-cause mortality by 26% (95% CI 3–43).[17] Warfarin is also significantly more effective than antiplatelet therapy with either aspirin alone (relative risk [RR] reduction 38 %, 95% CI 18-52) or dual antiplatelet therapy of aspirin and clopidogrel (RR 1.72, 95% CI 1.24-2.37 for antiplatelets versus warfarin) with only minor increase of ICH when compared against aspirin alone and no difference in rate of major bleeding when compared against dual antiplatelet therapy.[18]

Warfarin is also the more versatile oral anticoagulant that can be used in multiple clinical settings, which were omitted in the clinical trials on NOACs (e.g. severe renal failure, acute coronary syndromes in AF patients, etc) or were found to be unsuitable for anticoagulation with the NOACs (e.g. mechanical heart valves). Therefore, maintenance and further development of services for INR control to improve safety and efficacy of warfarin therapy is still warranted. Also, while use of the NOACs is prioritised over warfarin according to European guidelines, the American guidelines do not give preference to the NOACs over (well controlled) warfarin.[1,2]

In 'real world' clinical practice, the efficacy and safety of warfarin may be lower[19] as the limitations of warfarin therapy often result in its underuse and poor quality of anticoagulation control[20,21] evaluated as TTR. The lowest rate of strokes, systemic embolism and bleeding events is observed in patients with high TTR (e.g. >70%) and, vice versa, warfarin therapy but with poor TTR eventually results in increased risk of complications, with the patient having worse outcomes than if left untreated.[22,23] Common clinical risk factors can be related to TTR, as recently reported by Apostolakis et al.[24]

Thus, 'switching' anticoagulation from warfarin to NOACs is likely to be beneficial in patients with poorly controlled warfarin, with low TTRs, particularly if this is evident from patients' experience of being on warfarin. However, this hypothesis has not been tested in any controlled trial yet. It is also challenging how to choose appropriate anticoagulation option(s) in anticoagulation-naïve patients because variability of anticoagulant effect of warfarin confers increased risk of bleeding during initial time, hence, 'trial' period with warfarin should be avoided. The SAMe-TT_2R_2 score (Table 1) was introduced to answer if patient is expected to do well on warfarin (i.e. to maintain good TTR, those with score of 0 to 1) or not (those with score ≥2).[25,26] Regardless of the choice of anticoagulation, adherence factors related to education, geographic and cultural factors, social diversity, economics, and transportation as well as access to medical care from qualified clinicians, medical comorbidities, genetic variation should be considered.

The NOACs have specific single targets in coagulation cascade (Figure 1).[27] Dabigatran inhibits the enzymatic activity of thrombin (both free and clot-bound thrombin) that affects thrombin functions: conversion of fibrinogen to fibrin and its stabilization; activation of coagulation factors V, VIII, XI, and XIII; activation of platelets, inhibition of fibrinolysis, proinflammatory changes.[28] Rivaroxaban, apixaban, and edoxaban inhibit enzymatic activity of factor Xa (both free and within prothrombinase complex) that eventually leads to downstream blockade of prothrombin to thrombin conversion.[27]

In summary, the direct, dose-related, reversible inhibition with the NOACs together with few drug and food interactions lead to stable, rapidly attainable anticoagulation effect with

no necessity for long and complicated process of dose adjustment and regular INR monitoring (Table 2). Pharmacological properties of the NOACs in comparison to warfarin are summarised in Table 3.

Randomised clinical trials with NOACs for stroke prevention in AF

Four large phase III prospective randomized clinical trials, competing safety and efficacy of NOACs to warfarin, have been completed: RE-LY with dabigatran[30,31], ROCKET AF with rivaroxaban[32], ARISTOTLE with apixaban[33], and ENGAGE AF – TIMI 48 with edoxaban[34] (Tables 4 and 5).

Trials on the oral direct factor Xa inhibitors were double-blind[32-34], whereas the trial with dabigatran was open label between dabigatran and warfarin arms, but double blind between 2 arms with different doses of dabigatran (150 mg bid versus 110 mg bid).[30]

There have been much discussion of pros and cons of two designs in anticoagulation trials. Both of them have some strengths and weaknesses at different levels and to different degree. Therefore trial design should not be considered as the only or main factor influencing analysis and interpretation of trial findings.[35,36] For example, prospective randomized controlled trials using double-blinding of investigators and patients with respect to the actual treatment allocation may well be the gold standard in trial methodology, but are also more complex and highly motivated and/or compliant patients may be enrolled. On the contrary, open-label trials are relatively simpler and involve more representative of real clinical practice population and arguably are more generalizable. Even with open-label

design trials are subjected to selection (and other) bias.[34-36] Data from observational trials and real-world cohorts are also needed to enhance the evidence on 'new' treatment.

There were more enrolled patients with prior history of stroke, TIA or systemic embolism (and, hence, higher stroke risk according to the $CHADS_2$ score), and a lower mean TTR in the ROCKET AF (55%).[30,32-34] Thus, even in the idealized settings of clinical trials commencing and continuing warfarin can be challenging since INR remained in the suboptimal range in many patients treated with warfarin.

Discontinuation rates were higher in both dabigatran arms in comparison to warfarin arm in the RE-LY trial, whereas it was broadly similar for factor Xa inhibitors and warfarin in all other trials, that was related to higher rate of gastrointestinal adverse reactions.[30,32-34] High discontinuation rate and poor medication adherence is frequently found with pharmacological therapy, particularly for chronic conditions. The problem is complex and multifactorial, but many factors related to low adherence are common for chronic diseases, including stroke prevention with oral anticoagulation in AF patients. Educational level, smoking, working status, disability, indication for thromboprophylaxis, prior warfarin therapy, lower cognitive function, low scores on the mental component of the SF-36 health survey and poor baseline health appeared to be independent predictors of non-adherence to warfarin.[38] Overall these factors can be extrapolated to non-adherence to the NOACs. It is not a rare case when no apparent reason for drug discontinuation can be given by patient.[39-40]

Non-requirement for regular laboratory assessment and BID administration (for dabigatran and apixaban) were concerned to be reasons of poorer compliance with the NOACs in comparison to warfarin. One missed dose of a NOAC with moderate half-life (approx. 10-12 hours) might eventually lead to adverse outcomes with higher probability than one missed dose of warfarin given the shorter half-life of most NOACs. For a drug with an 11 hour half-life, for example, missing one dose on a once-daily (qd) regime is pharmacokinetically similar to missing 3 doses on the twice-daily (bid) regime.[41]

Overall, in the meta-analysis of randomised controlled trials, discontinuation rate with NOACs was found not to be statistically different in comparison to pharmacologically active comparators (e.g. warfarin or aspirin) in patients with AF. When causes of discontinuation were analysed separately, no difference was observed with respect to discontinuation due to adverse events or consent withdrawal (rates of discontinuation for non-adherence were not reported).[42] Indeed, discontinuation rate particularly due to non-adherence may be higher when outwith of trial setting. Therefore, patients' education is of paramount importance.[43-45]

All studies shared similar primary efficacy (stroke or systemic thromboembolism) and safety (major bleeding) end points apart from the ROCKET-AF trial, in which primary safety end point included major and clinically relevant non-major bleeding.[30-34] With respect to the primary efficacy end point all NOACs were shown to be at least non-inferior to warfarin (low dose dabigatran, rivaroxaban, and both doses of edoxaban) or even superior to warfarin (high dose dabigatran, apixaban).[30-34] Treatment with dabigatran 150 mg bid resulted in significantly lower rate of ischaemic stroke and cardiovascular mortality.[30,31] The latter was

lower with both edoxaban doses as well.[34] Apixaban and low dose edoxaban were associated with reduced all-cause mortality, however, edoxaban 30 mg qd appeared to be less protective against ischaemic stroke.[33,34]

There was a non-significant trend towards higher rate of myocardial infarction with both doses of dabigatran.[31] One explanation for this is that therapeutic concentration of dabigatran, which is protective in chronic setting, was perhaps insufficient to inhibit increased amount of thrombin within ruptured/erosed coronary plaque.[46] On the contrary, warfarin leads to decreased of several coagulation factors as well as factor Xa inhibitors allow upstream inhibition of coagulation cascade (one inhibited molecule of factor Xa prevents conversion of approximately 1000 molecules of prothrombin to thrombin).

In terms of safety, both doses of edoxaban, low dose dabigatran and apixaban were significantly better than warfarin, while rivaroxaban and high dose of dabigatran were non-inferior.[30-34] All the NOAC trials found a lower rate of both haemorrhagic stroke and ICH with NOACs compared to warfarin.[30-34] High dose dabigatran and edoxaban as well as rivaroxaban were associated with increased rate of gastrointestinal bleeding that was probably due to their metabolism via P-gp (permeability glycoprotein) efflux transporter, expressed in intestine and therefore resulting in locally higher concentrations of NOACs.[30-32,34] In terms of the mortality end point, both dose regimes of edoxaban and high dose dabigatran were associated with lower rate of death from cardiovascular causes as well low dose edoxaban and apixaban were associated with lower rate of death from all causes when compared to warfarin.[30,31,33,34]

Data regarding NOACs efficacy and safety were pooled in several systematic reviews and meta-analyses (Table 6), across all of which results were consistent: NOACs were found to be superior to warfarin with respect to prevention of stroke and systemic embolism, haemorrhagic stroke, ICH, and all-cause mortality; non-inferior with respect to rate of ischaemic stroke and myocardial infarction.[47-50] There was a trend towards reduced risk of major bleeding. As discussed above, anticoagulation with NOACs resulted in more episodes of gastrointestinal bleeding.[47,50]

When efficacy and safety of the NOACs in comparison to warfarin were modelled in the large Danish 'real world' AF population, the net clinical benefit for all the NOACs (data on edoxaban were not included into this analysis) favoured their use in all patients with the $CHADS_2$ score ≥1 or CHA_2DS_2-VASc score ≥2 irrespective of bleeding risk, with the greatest seen in patients with higher stroke and bleeding risk.[10] Within the post-marketing assessment of the efficacy and safety of NOACs dabigatran and rivaroxaban showed consistent with their pivotal trial results.[51,52]

Once-daily versus twice-daily dosing for the NOACs

There areconcerns if in AF safety and efficacy of once daily regime (rivaroxaban and edoxaban) was the same to twice daily regime (dabigatran and apixaban) since all the NOACs have broadly similar and overlapping half-life times. Typically, qd dosing results in a greater maximum plasma concentration (C_{max}) and lower or similar minimum plasma concentration (C_{trough}) in comparison to bid regime dosing with the same total daily dose.[53] However, the pharmacological profile of the drug, taken alone, is not sufficient to make a

decision on optimal dosing regime. Indeed, balancing efficacy and safety is far beyond C_{max}-C_{trough} interplay. Nevertheless, pharmacodynamics of the NOACs (i.e. extent of anticoagulation effect) largely depends on its pharmacokinetics with maximum effect at C_{max} (which is also related to risk of bleeding) and minimum effect at C_{trough} below which anticoagulant effect is not sufficient and therefore related to risk of thromboembolic complications. However, this assumption was found not to work with all the NOACs.[53]

The qd dosing of rivaroxaban was discovered via pharmacokinetic modelling based on pharmacokinetic data from the two phase II venous thromboembolism trials. C_{max} was approximately 20% higher and C_{trough} was approximately 60% lower with qd dosing when compared with bid dosing, however, the 5^{th}–95^{th} percentile ranges for both parameters were overlapping. Thus, a bid dosing of rivaroxaban might not provide more stable drug levels in the blood and anticoagulation effect.[54] Better patient adherence to oral anticoagulation with the qd regime was also considered.

In a phase II trial and pharmacological modelling study with edoxaban lower bleeding rates were associated with qd dosing compared with bid dosing of the same total daily dose of 60 mg. Significant correlation was observed between bleeding rates and C_{trough} but not C_{max} and thus, a qd dosing regime was selected for the phase III ENGAGE AF - TIMI 48 trial.[55,56]

In the meta-analysis of qd versus bid dosing the latter was found to be beneficial for stroke and systemic embolism prevention with dabigatran 150 mg (HR 0.75, 95% CI 0.58–0.96) but not for apixaban versus qd common estimate (rivaroxaban 20(15) mg and edoxaban 60(30) mg) as well as for ICH prevention with bid common estimate versus rivaroxaban (HR 0.57,

95% CI 0.37–0.88) but not versus edoxaban. Thus, bid dosing has somewhat better risk-benefit profile, but that may not not the case for all the NOACs.[57]

Monitoring of anticoagulant activity with the NOACs

Unfortunately, the available routine anticoagulation assays only provide clinicians with a qualitative assessment of anticoagulant effect with NOACs (Table 3).[58] In terms of monitoring for the NOACs, all have been approved for use in AF patients without necessity for regular laboratory testing assuming a stable anticoagulation effect. However, a recent analysis of dabigatran trough plasma concentrations in a subgroup of patients from the RE-LY trial in relation to their outcomes triggered extensive discussion of the pros and cons of dose adjustment based on concentration monitoring.[59-61]

In the analysis by Reilly et al, concentration of dabigatran was found to be associated with age, kidney function, weight, and female gender.[62] Over five-fold difference of concentration was observed between the 10th and 90th percentiles with either dose of dabigatran. Also, a proportion of patients appeared to have very low (and, hence, decreased stroke protection) or very high (and, hence, increased bleeding risk) plasma level of dabigatran.[62] Such a drug level variability translates into concentration-dependent increase of rate of bleeding events. Nonetheless, the rate of stroke and systemic embolism appeared to be less affected within therapeutic range.[62] Thus, authors suggested that laboratory guided adjustment of dabigatran dose might result in further improvement of its safety and efficacy in AF in comparison to fixed doses, at least in selected patients at higher risk (e.g. elderly and/or those with renal dysfunction).[62]

On the contrary, results of mathematical modelling attempted to test the utility of dabigatran dose adjustments via measuring its plasma level did not support this strategy, because the simulations did not seem to allow reliable prognosis for actual patients' outcomes.[63] The variability of dabigatran concentrations when considered together with the RE-LY trial results reflects its wide therapeutic range in which it remains effective and safe rather than carries inevitable threat to AF patients. Also, assays for evaluation of dabigatran concentration are not availably routinely making this approach complicated for everyday clinical practice. Oral Factor Xa inhibitors may be less subject to concentration variability, as observed for dabigatran, due to their higher bioavailability in comparison to dabigatran and also lower dependence on renal clearance (Table 3).

Thus, whether regular laboratory control and concentration-based dose adjustment of dabigatran (and other NOACs) will bring additional benefits in comparison to current fixed dose approach without monitoring requires further clarification in controlled trials.

Consistency of the NOACs across patients' subgroups

Data on overall efficacy and safety of the NOACs obtained from landmark trials appeared to be consistent across patients' subgroups (Table 7). There were no statistically significant interactions shown among subgroups based on age[34,64-66], $CHADS_2$ score[32,34,67,68], kidney function[32,69,70], symptomatic heart failure[32,34,71,72], prior stroke or TIA[34,73-75], concomitant use of antiplatelet drugs[32,76,77], and centre average TTR[34,78-80] with respect to the primary efficacy end point. Data on subgroups according to kidney function and antiplatelet therapy use for edoxaban are not available as yet. While there was no significant interaction

between VKA-naïve and VKA-experienced AF patients for dabigatran, rivaroxaban, and apixaban[30,32,81]; however, edoxaban did significantly better in the subgroup of VKA-naïve patients.[34]

There was also no interaction across majority of specified subgroups with respect to major bleeding. Lower (but non-inferior) efficacy of either dose of dabigatran in patients aged ≥75 years was found.[64] However dabigatran still had a favourable safety profile for ICH in elderly AF patients in comparison to warfarin (RR 0.37, 95% CI 0.21-0.64, and RR 0.42, 95% CI 0.25-0.70 for dabigatran 110 mg bid and 150 mg bid, respectively).[64] Age does not apply any particular limitations with respect to NOACs use, although age-related decline in renal function, risk of falls, anaemia, and other multiple comorbidities should be considered.[82]

In the meta-analysis of AF and non-AF randomised controlled trials risk of major or clinically relevant non-major bleeding did not differ between elderly patients (≥75 years old) taking one of the NOACs and those on conventional therapy or taking active comparator (warfarin, aspirin, or enoxaparin). Among AF patients risk of stroke or systemic embolism favoured use of the NOACs in elderly patients (OR 0.65, 95% CI 0.45-0.87).[83] In young patients AF often represents primarily electrical disorder and in the absence of stroke risk factors usually no oral anticoagulation is required, however if this is not the case, the safety and efficacy of the NOACs is unlikely to be worse than in the RE-LY trial and 'real-world' data. Use of the NOACs in younger patients is feasible at least in respect to quality of life since they do not apply so many restrictions and limitations as warfarin does, therefore allowing enhanced lifestyle.

Also, apixaban appeared to be safer than warfarin irrespectively of kidney function, but the largest reduction in bleeding complications was achieved in patients with estimated glomerular filtration rate below 50 mL/min.[70]

There was no significant interaction between centre average TTR and major bleeding when comparing 150 mg dabigatran and rivaroxaban with warfarin, although there was a tendency to less bleeding events at lower average centre TTR; also, no significant interactions with centre TTR were found for ICH with both dabigatran regimes and rivaroxaban.[78,79]

All NOACs were found to have similar to warfarin efficacy and safety if cardioversion of AF to sinus rhythm was necessary during study follow-up.[84-86] Similar to warfarin management during pericardioversion period apply to the NOACs (i.e. therapeutic anticoagulation 3 weeks before and 4 weeks after procedure). In general, transoesphageal echocardiography is not compulsory prior to cardioversion if patient was appropriately anticoagulated, unless there are doubts about patient adherence to treatment, since no routine tests are available to screen patients compliance while preparing for procedure.[1,2,7]

NOACs in patients presenting with acute coronary syndrome and or undergoing percutaneous intervention

AF and coronary artery disease (CAD) frequently coexist. Approximately 30% of AF patients have CAD, and approximately 15% of the latter undergo stent implantation.[87]

Presence of vascular disease, particularly complicated one (e.g. history of myocardial infarction, revascularisation, etc.) confers additional risk of stroke in AF patients, and therefore has been incorporated into the CHA_2DS_2-VASc score.[8]

According to current recommendations in patients with AF and stable CAD oral anticoagulation either with the NOACs or dose-adjusted VKA is sufficient alone.[88] No antiplatelets are required in addition to oral anticoagulation since in non-acute setting there is no significant reduction in the risk of coronary events or stroke and systemic embolism, whereas risk of bleeding is increased significantly (HR 1.50, 95% CI 1.23-1.82 with aspirin and HR 1.84, 95% CI 1.11-3.06 with clopidogrel).[89] On the contrary, in patients with acute coronary syndrome (ACS) and/or undergoing percutaneous intervention (PCI) and stenting, combination of oral anticoagulation and antiplatelet therapy is needed to protect from both stroke and systemic embolism, and stent thrombosis since both pathways are activated (i.e. coagulation and platelet activation).[90,91]

The choice and duration of the use of combination treatment depends on the clinical setting of coronary intervention (elective PCI stable CAD or primary one in ACS) and baseline stroke and bleeding risk.[88] While previously bare metal stents (BMS) were recommended in order to reduce duration of triple therapy in comparison to (old generation) drug eluting stents (DES)[92], new generation DES do not have any particular disadvantages to BMS with respect to major adverse events including composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or target-lesion revascularisation.[88,93,94]

In terms of NOACs use in this group of patients, the data are limited since patients after ACS, myocardial infarction or receiving dual-antiplatelet therapy were excluded from the AF trials and vice versa patients with AF were excluded from the ACS trials. As discussed above no difference with respect to the NOACs efficacy was observed between patients who did take antiplatelets during trial period concomitantly with oral anticoagulant and those who did not as well as there was broadly similar increase of major bleedings when combination of oral anticoagulation and antiplatelet drugs was used.[32,34,76,77]

Several ACS trials (AF patients were excluded) with the NOACs were performed. Two regimes of rivaroxaban were studied in the phase III ATLAS ACS 2–TIMI 51 trial (2.5 mg bid and 5 mg bid) which were found to have the most favourable efficacy/safety profile in the phase II ATLAS ACS–TIMI 46 trial.[95,96] Rivaroxaban significantly reduced the primary efficacy end point (death from cardiovascular causes, myocardial infarction, or stroke), when added to standard dual antiplatelet therapy as compared with placebo, irrespectively of dose: HR 0.84, 95% CI 0.72–0.97 for 2.5 mg BID regime and HR 0.85, 95% CI 0.73–0.98 for 5 mg bid regime.[95] The lower dose of rivaroxaban was also associated with the reduction of mortality end points: HR 0.66, 95% CI 0.51–0.86 for c cardiovascular mortality and HR 0.68, 95% CI 0.53–0.87 for all-cause mortality.[95] Nonetheless, better efficacy of triple therapy was achieved at cost of higher rate of major bleeding and ICH.[95]

In the phase III APPRAISE-2 trial apixaban 5 mg bid in addition to standard antiplatelet therapy was tested. Notwithstanding trend towards lower rate of ischemic events with the 2.5 mg bid and 10 mg qd regimes in the phase II APPRAISE trial, particularly when apixaban was added to aspirin monotherapy; no reduction in recurrent ischemic events but significant

increase in bleeding events, including fatal bleedings and ICH was observed in the APPRAISE-2 in comparison to placebo irrespectively of antiplatelet therapy (aspirin monotherapy or aspirin with clopidogrel).[97,98] Similarly, dose-dependent increase of major bleeding or clinically relevant non-major bleeding with no significant impact on rate of ischaemic events was observed in patients after myocardial infarction in the phase II RE-DEEM trial with dabigatran.[99]

Thus, in patients with a recent ACS, addition of one of the NOACs to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase in bleeding, most pronounced when NOACs are combined with dual antiplatelet therapy.[100] Because rivaroxaban dose regimes were different from those in AF trials and since AF patients were excluded the data from ACS trials cannot be directly extrapolated to AF patients who develop ACS and/or undergo stenting.

In summary, oral anticoagulation has to be continued if it was indicated for stroke prevention in AF when AF precedes development of ACS. Also, there is no reason to make changes into already established anticoagulation regime either with one of the NOACs or well-adjusted VKAs in each individual patient in acute setting. In ACS-first patients who develop new onset AF while taking dual antiplatelet therapy, oral anticoagulation should be initiated. In the absence of randomised trials no preference is given to any of available anticoagulants.[88] Given limited data on safety and efficacy of the NOACs as part of combination therapy with antiplatelet drugs in the setting of ACS and/or stenting as discussed above several trials have been designed to address these patients.

Periprocedural management of the NOACs

Oral anticoagulation in patients with AF and ≥1 stroke risk factor is life-long. Not infrequently the need for elective or urgent surgery may occur in anticoagulated patients. The latter poses them at higher risk of periprocedural bleeding complications and requires temporary interruption of treatment that in turn is associated with higher risk of stroke and thromboembolic events. The risk of periprocedural major bleeding varies depending on severity of tissue trauma during intervention.

This aspect has been further addressed in the "European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants"[7] and 9th ACCP antithrombotic therapy consensus[101], and three major bleeding risk categories of procedures (minimal, minor, and major procedures) were established.[102] Minimal procedures are those with little tissue trauma (superficial skin and oral mucosal surgery, including skin biopsies, wound revisions, non-extraction dental treatment).[102] Minor procedures were procedures with little tissue trauma, but relevant bleeding risk: transluminal interventions, pacemaker-related surgery, pleural and peritoneal puncture, eye surgery, endoscopy, laparoscopy, organ biopsies, dental extraction, hernia repair, and intramuscular and paravertebral injections.[102] Major procedures include surgery associated with significant tissue trauma and high bleeding risk: open pelvic, abdominal and thoracic surgery, brain, vascular, orthopaedic and trauma surgery.[102]

Minimal procedures can be performed at C_{trough} of the NOAC, i.e. 12-24 hours after the last intake for bid and qd dosing, respectively.[7] In case of minor or major procedures last dose of

the NOAC has to be taken 24 and 48 hours before intervention, respectively.[7] Pre-intervention termination of the NOAC should to be adjusted (extended) in patients with kidney dysfunction. Specific NOAC-free intervals have been suggested for each particular drug and degree of renal impairment.[7] In case of emergent surgery in patients anticoagulated with the NOACs it is recommended to postpone surgery as long as possible - at least 12 hours but ideally 24 hours after the last dose.[7] Oral anticoagulation can be restarted 6-8 hours after procedure with immediate and complete haemostasis. For procedures associated with immobilization reduced DVT prevention dose or intermediate dose of low molecular weight heparin can be used from 6–8 to 48-72 hours after surgery, and the NOAC restarted following heparin.[7]

In the Dresden registry (2179 patients of which 595 (27.3%) underwent 863 procedures) vast majority of procedures was classified as minor (74.3%) following by minimal (15.6%) and major (10.1%) procedures. Median duration of interruption of anticoagulation was 2 (interquartile range [IQR] 2) days before and 1 (IQR 3) day after the procedure, resulting in a total duration of NOAC interruption of 3 (IQR 6) days.[102]

Given the predictable pharmacokinetics/pharmacodynamics of the NOACs shorter interruption period and no bridging with heparin is required in comparison to warfarin. However, recent data indicate low adherence to this recommendation. As many as 30% of all procedures were performed with heparin bridging, that resulted in 5-fold higher risk of major bleedings.[102]

In the pivotal trials with the NOACs oral anticoagulation was interrupted in 25% of patients in the RE-LY trial for a surgical or invasive procedure[103], in 33% of patients in the ROCKET AF trial for various reasons[104], and in 34% of patients in the ARISTOTLE trial for invasive procedures.[105] Overall, no difference in thrombotic events rate was observed between the NOAC and warfarin arms: both doses of dabigatran (0.50% versus 0.50%), rivaroxaban and (0.30% versus 0.41%), and apixaban (0.43% versus 0.56%).[103-105] There was no difference in rate of major bleeding as well: 3.8% and 4.1% versus 5.6% for low and high dose of dabigatran versus warfarin; 0.99% versus 0.79% for rivaroxaban versus warfarin, and 1.55% versus 1.80% for apixaban versus warfarin.[103-105] In the Dresden registry ,irrespectively of the NOAC used major cardiovascular events developed in 1.0% of patients, and major bleedings occurred in 1.2% of patients.[102]

Standard haemostatic measures (compression, surgical haemostasis, fluid replacement) are sufficient to cure non-life-threatening bleeding, however, in life-threatening bleeding reversal agents (activated and non-activated prothrombin complex concentrate and recombinant factor VIIa) can be used (Table 3).[7,106,107] In patients with dabigatran-related bleeding, haemodialysis is also a useful option because of low protein binding and high water solubility of dabigatran.[108-110]

Continuation of the NOACs after thromboembolic and bleeding complications

Like in patients with stable therapeutic INR taking warfarin[111], notwithstanding stable anticoagulation effect with the fixed doses of the NOACs, there is still minor probability of the development of ischaemic stroke and other thromboembolic complications, particularly

in patients with high estimated stroke risk according to the CHA_2DS_2-VASc score. Given the history of stroke, TIA or systemic embolism even without other risk factors assigns patient into high risk stratum of stroke recurrence, apparently oral anticoagulation should be continued as soon as disease course gets stable.

However, some questions arise. Why did stroke (systemic embolism) develop despite appropriate anticoagulation? Taking into account absence of routinely available laboratory assays to measure achieved degree of anticoagulation with the NOACs, our knowledge of anticoagulation efficacy in each individual case is based on assumption that patient takes drug regularly. Thus, much attention has to be paid to ensure patient's compliance. Educational programs are of paramount importance to increase patient adherence to treatment.[43-45]

Also, other thromboembolism risk factors has to be checked and modified if possible (obviously, as part of primary rather than secondary prevention). For example, obesity is an independent risk factor of stroke development both in patients without AF and in those with arrhythmia.[112,113] Indeed, overweight and obesity are associated with a 31% and 36% higher risk of ischaemic stroke, thromboembolism, or death adjusted for the CHA_2DS_2-VASc score , respectively, among participants of the prospective Danish Diet, Cancer and Health study.[113] Heavy smoking was found to confer significantly increased independent of the CHA_2DS_2-VASc score risk of thromboembolism or death with hazard ratios of 3.64 and 2.17 for females and males respectively.[114] Similarly, excess alcohol intake (>27 drinks per week for males and >20 drinks per week for females versus <14 drinks per week) resulted in 33% and 23% higher risk of thromboembolism or death.[115]

While patient compliance has been ascertained, patient might be screened for hereditary and acquired haemostatic thrombophylic disorders, e.g. factor V Leiden, prothrombin G20210A variant, protein C, S, antithrombin III deficiency, dysfibrinogenaemia, antiphospholipid syndrome, malignancy, myeloproliferative disorders, oestrogen replacement therapy, in which the NOACs were not tested and might not provide sufficient anticoagulation effect with dosages recommended for stroke prevention in non-valvular AF.[7,116] Nonetheless, it is unknown whether routine screening for thrombophilic states in patients with ischemic stroke or TIA is useful and therefore it is not recommended to be performed on a routine basis.[117]

The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.[117] The NOACs might be beneficial in patients who had history of poorly controlled INR (i.e. low TTR). Among the NOACs, factor Xa inhibitors can be switched to dabigatran that was found to be superior to warfarin for ischaemic stroke prevention while factor Xa inhibitors were only non-inferior to warfarin. Vice versa, direct thrombin inhibitor dabigatran can be switched to rivaroxaban, apixaban or edoxaban if there are concerns on decreased dabigatran bioavailability and hence low trough plasma concentration (or pharmacogenetic variant associated with lower dabigatran bioavailbility) because factor Xa inhibitors are all characterized with a higher bioavailability and therefore are likely to be less subjected to plasma concentration drop.[118,119]

When to reinitiate oral anticoagulation? Continuation of oral anticoagulation including the NOACs after ischaemic stroke is recommended within 14 days after the onset of neurological symptoms.[117] However if the risk of haemorrhagic conversion is high, which dependent on the infarct size, quality of hypertension control, or there is an evidence of haemorrhagic transformation on initial imaging resumption of anticoagulation should be extended beyond this time threshold.[117] One approach is based on the 1-3-6-12 day rule that means resumption of anticoagulation after 1 day in patients with TIA; after 3 days in patients with small, non-disabling infarct; after 6 days in patients with a moderate size stroke; and after 12 days (2-3 weeks) in patients with large strokes.[7]

The decision on oral anticoagulation in patients who developed ICH is even more challenging. According to the current labelling recent ICH is a contraindication for the oral anticoagulants either with the NOACs or VKAs. The risk of ICH recurrence and stroke development related to anticoagulation resumption or withholding should be balanced based on individual characteristics.[120]

In the BRAIN study (67% of patients with AF) warfarin reinitiation during the hospital stay (median 19.7 days) did not lead to higher bleeding and mortality rate.[121] The rate of thrombotic complications did not differ between groups as well. The factors related to decision to resume anticoagulation were lower stroke severity and presence of prosthetic heart valves.[121] On the contrary, study of Majeed et al showed higher rebleeding rate or expansion of ICH (14% versus 8%) but lower rate of thrombotic complications (2% versus 18%) in patients who continued to take warfarin (median time from ICH development 5.6 weeks, 56% of patients in study were those with AF).[122] Importantly, therapeutic INR and

high TTR do not guarantee event-free survival if anticoagulation was resumed.[121,122,123] The most important risk factor, affecting probability of ICH recurrence and hence safety of anticoagulation resumption, is its location. Patients with lobar location of ICH have a higher risk of rebleeding compared to those with deep hemispheric bleeding (e.g., basal ganglia, thalamus, or brainstem).[124-126] The rate of ICH recurrence after lobar ICH varied substantially between studies from 4.4% to 22%; however it was higher than recurrence rate after deep hemispheric bleeding (2.1-4%) across all studies.[124-126] It was suggested that baseline stroke risk should correspond to stroke rate of 6.5% or more (i.e. CHA_2DS_2-VASc score of 5 or higher) and risk of ICH recurrence should correspond to ICH rate less than 1.4% to trade off benefits and hazards of anticoagulation.[124]

Robust evidence to provide guidance in this clinical setting is sparse.[127,128] RCTs have not been performed to address this treatment dilemma. In the absence of randomized trials there are no firm recommendations as well. Anticoagulation after non-lobar ICH (antiplatelet therapy after all ICH) might be considered while avoidance of long-term anticoagulation is probably recommended after spontaneous lobar ICH in patients with non-valvular AF.[127,128] Another markers have been suggested, like cerebral microbleeds on MRI and apolipoprotein E gene polymorphism, however their utilization for decision making has not been tested as well.[129,130]

All the NOACs were found to cause significantly less ICH than well controlled warfarin.[30-34] Thus, in patients, which are eligible for resumption of anticoagulation because of high stroke risk, the NOACs might be a reasonable alternative to warfarin despite there were no studies which specifically addressed this subset of patients.

In terms of other common bleeding locations, e.g. gastrointestinal bleeding, oral anticoagulation can be safely continued, however, no guidance when to resume therapy has been provided as well.[131] Indeed, Qureshi et al. reported that restarting warfarin after 7 days of bleeding was more favourable than after 1 months since it was associated with decreased thromboembolism (HR 0.71, 95% CI 0.54-0.93) and reduced mortality (HR 0.67, 95% CI 0.56-0.81) but not recurrent gastrointestinal bleeding (HR 1.18, 95% CI 0.94-1.10).[132] These results appeared to be consistent with earlier data.[133]

Careful evaluation of the cause of bleeding is of particular importance. For example, gastrointestinal bleeding may unmask pre-existing gastrointestinal tumours, which otherwise (without anticoagulation therapy) would be asymptomatic for a long time.[134] Available data came from the warfarin studies. Given the higher risk of gastrointestinal bleeding with the NOACs than with warfarin, similar time frame (i.e. 7 days) should not be extrapolated directly to patients taking one of the NOACs.

Tailoring anticoagulation to the patient using NOACs

The NOACs changed the landscape of stroke prevention in AF patients. However all NOACs are not the same as well as landmark trials on NOACs were not homogeneous (particularly, ROCKET AF), and meta-analyses underscoring their favourable efficacy and safety profile do not supply clinicians with an algorithm which NOAC to choose in a particular clinical situation.

How does one NOAC agent compare against another? This can only be answered with a head to head trial, but such a trial would be huge and expensive, and unlikely to be performed. As an alternative, indirect comparisons have been performed, using warfarin as a common denominator, notwithstanding the various limitations of such methodology. [135]

No significant differences in efficacy end points including mortality were noted between apixaban and dabigatran (both dosages) or rivaroxaban.[49] Dabigatran 150 mg bid was associated with lower risk of stroke and systemic embolism (HR 0.74, 95% CI 0.56–0.97), haemorrhagic stroke (HR 0.44, 95% CI 0.20–0.96) and non-disabling stroke (HR 0.60, 95% CI 0.37–0.97) compared to rivaroxaban. [49] Apixaban was associated with less major bleedings compared with dabigatran 150 mg bid (HR 0.74, 95% CI 0.61–0.91) and rivaroxaban (HR 0.66, 95% (0.54–0.81), but not significantly different from dabigatran 110 mg bid which was also safer than rivaroxaban (HR 0.77, 95% CI 0.63–0.94). [49] The results were consistent with one more indirect comparison of dabigatran, rivaroxaban and apixaban. [136]

Separate comparisons for primary and secondary stroke prevention was carried out by Rasmussen et al., who found apixaban to be superior to dabigatran 110 mg bid for certain types of stroke (HR 0.59, 95% CI 0.36-0.97), and to dabigatran 150 mg bid, resulting in less major (HR 0.75, 95% CI 0.60-0.94) and gastrointestinal (HR 0.61, 95% CI 0.42-0.89) bleedings, but less protective against any type of stroke (HR 1.45, 95% CI 1.01-2.08) when compared with the high dosage dabigatran. [137] For secondary prevention of stroke, no significant differences in safety and efficacy between dabigatran 150 mg, rivaroxaban, and apixaban were found apart from a less myocardial infarctions with apixaban in comparison to high dosage of dabigatran (HR 0.39, 95% CI 0.16-0.95) and less haemorrhagic stroke (HR

0.15, 95% CI 0.03-0.66), vascular death (HR 0.64, 95% CI 0.42-0.99), major bleeding (HR 0.68, 95% CI 0.47-0.99), and ICH (HR 0.27, 95% CI 0.10-0.73) with the low dosage of dabigatran versus rivaroxaban.[137]

The most recent indirect comparisons included also data on edoxaban 30 mg qd and 60 mg qd.[138,139] High dose edoxaban was found to be associated with higher rate of stroke and systemic embolism, stroke and haemorrhagic stroke in comparison to dabigatran 150 mg bid, and to cause less major bleedings than rivaroxaban, but more major or clinically relevant non-major bleedings and gastrointestinal bleedings than apixaban.[138,139] Low dose edoxaban appeared to be less effective for stroke and systemic embolism, any stroke and ischaemic stroke than all NOACs but dabigatran 110 mg bid.[138,139] However lower dose edoxaban was associated with significantly reduced rate of major bleeding (compared to all NOACs) and gastrointestinal bleeding (compared to all NOACs but apixaban).[138,139] Either dose regime of edoxaban did not differ from other NOACs with respect to ICH and mortality end points.[138,139]

Given the available data on NOACs, anticoagulation regimen in patients with non-valvular AF can be tailored to each individual case, considering the risks and the benefits, side effects, comorbidities, and patients' preferences. Thus, we can fit the drug to the patient (and vice versa). For example, high dose dabigatran, given its superiority over warfarin for ischaemic stroke prevention, might be considered in patients with the high CHA_2DS_2-VASc score, but if patients also have a high bleeding risk (e.g. HAS-BLED ≥3), apixaban, dabigatran 110 mg bid or edoxaban is preferred. Dabigatran is associated with gastrointestinal side effects; hence, oral factor Xa inhibitors might be used instead in patients with dyspepsia.

Low dose dabigatran or edoxaban and dose adjustment of apixaban and edoxaban should be considered in patients with kidney diseases, depending on their renal function. Where patients may prefer a once daily regimen of anticoagulation, thus, rivaroxaban and edoxaban allow this.

Future directions

Ongoing clinical trials

A large body of evidence supporting safety and efficacy of the NOACs for stroke prevention in AF is already available, but many questions in terms of use of NOACs in specific clinical settings (cardioversion and ablation of AF, concomitant use with antiplatelet drugs in patients with coronary artery disease undergoing stenting, severe kidney dysfunction, etc.) remain not answered because of limited evidence from post-hoc or prespecified analysis of subgroups or exclusion from the landmark trials.

Many clinical trials have been initiated to overcome these gaps in data. Cardioversion of AF to sinus rhythm is associated with an increased risk of thromboembolic complications, and therefore even low risk patients require pericardioversion anticoagulation. Safety and efficacy of the NOACs for this purpose is studied in X-VERT and ARC trials with rivaroxaban[140,141], EMANATE with apixaban[142], and ENSURE-AF with edoxaban[143].

Ablation of AF is increasingly used in arrhythmia management. Apart from patient's background stroke risk it is associated with additional risk of thrombogenesis due to presence of foreign bodies in the circulation and occurrence of areas of stasis produced by them; denaturation of blood proteins; endothelial damage; atrial stunning caused by

ablation, etc. Oral anticoagulation using dabigatran (DAPPAR AF[144], ODIn-AF[145], and one trial from Vanderbilt University[146]) and rivaroxaban (VENTURE-AF[75147], OCEAN[148]) are being evaluated in patients, which undergo AF ablation therapy. Because left atrial appendage (LAA) is considered to be the main source of thrombi in AF, efforts were directed towards determining the effect of the NOACs on LAA thrombus resolution, for example, in the X-TRA trial with rivaroxaban.[149]

To study whether the NOACs have the same efficacy and safety as warfarin conventionally used as part of triple therapy in patients with AF undergoing PCI, is the purpose of the REDUAL-PCI trial with dabigatran[150], and PIONEER AF-PCI[151] and REWRAPS[152] with rivaroxaban. It is also challenging when to restart oral anticoagulation in patients following acute ischaemic stroke because of increased risk of stroke recurrence as well as ICH. The RELAXED[153] and TripleAXEL[154] studies have been designed to assess safety and efficacy of rivaroxaban in AF patients with acute ischaemic stroke. While dabigatran 75 mg bid received FDA approval in severe kidney dysfunction (CrCl 15-30 mL/min) this was based on pharmacokinetic modelling and simulation. Thus, this regime is currently undergoing testing in a clinical trial.[155]

Importantly, NOACs can be used in non-valvular AF, which is defined by European guidelines as AF in the absence of rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[1] The American guidelines also include bioprosthetic heart valves and mitral valve repair, as 'valvular AF'.[2] Valvular AF was an exclusion criterion in the pivotal NOAC trials. Indeed, the RE-ALIGN trial of dabigatran in patients with heart valve replacement was terminated prematurely due to excess of thromboembolic and bleeding

events among patients in the dabigatran arm compared with warfarin.[156] However, a new pilot trial with dabigatran has been initiated to study its safety and efficacy in patients with mitral and/or aortic bioprosthetic valves (DAWA study).[157]

Antidote programme

One of important limitations of the NOACs is absence of antidote to reverse anticoagulation when necessary. Activated or non-activated prothrombin complex concentrates can be used instead. Nonetheless, specific antidotes have been developed and are currently being tested in clinical trials.

Idarucizumab, a fully humanized antibody fragment (Fab) was developed as a specific antidote for dabigatran. [158] It is structurally similar to thrombin, but its affinity for dabigatran is approximately 350 times higher than for thrombin. Idarucizumab does not to bind to known thrombin substrates, and does not affect coagulation or platelet aggregation assays. Idarucizumab can reverse dabigatran activity within one minute of intravenous injection. Patients with uncontrolled bleeding or requiring emergency surgery or procedures are treated with idarucizumab in an ongoing phase 3 clinical trial RE-VERSE AD (A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran).[159]

Andexanet α, modified recombinant factor Xa have been developed as an antidote for factor Xa inhibitors.[160] Andexanet α acts as a factor Xa decoy catching circulating factor Xa inhibitor, hence, allowing intrinsic factor Xa to escape inhibition and take part in the coagulation cascade. Andexanet α is enzymatically inactive due to several modifications in comparison to normal factor Xa, for example, being unable to cause prothrombin activation

and to bind to phospholipids in the prothrombinase complex. This agent works in a dose-dependent manner, and several Phase 3 studies have been designed to study ability of andexanet α to reverse anticoagulation effect of currently available oral factor Xa inhibitors.[161,162]

Conclusion

With the introduction of NOACs, the landscape of oral anticoagulation for stroke prevention in patients with non-valvular AF had undoubtedly changed. Given the availability of different agents, clinicians currently have a choice not only between VKAs and NOACs, but inside NOAC class as well, tailoring oral anticoagulation to the patient. Further randomised clinical trials as well as 'real world' data will help with better understanding of NOACs' pros and cons in AF.

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Table 1. Practical tools to assess risk of stroke and major bleeding, and quality of anticoagulation with warfarin in patients with AF

Risk factor	CHA_2DS_2-VASc score[8]	Risk factors	HAS-BLED score[15]	Risk factors	SAMe-TT_2R_2 score[24]
Congestive heart failure/LV dysfunction	1	Hypertension (systolic blood pressure >160 mm Hg)	1	Sex category (i.e. female gender)	1
Hypertension	1	Abnormal renal and / or liver function	1 or 2	Age <60 years	1
Age ≥75 years	2	Stroke	1	Medical history (≥2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary, hepatic or renal disease)	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1	Treatment with interacting drugs (e.g., amiodarone)	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1	Tobacco use (within 2 years)	2
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g.,>65, frail condition)	1	Race (i.e. non-caucasian)	2
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2		
Sex category (i.e. female gender)	1				
Maximum score	9	Maximum score	9	Maximum score	8

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral artery disease; TIA/TE, transient ischemic attack/thromboembolism

Table 2. Pros and cons of the NOACs

Pros	**Cons**
Wide therapeutic window, predictable anticoagulation response with standard doses	No specific antidote available
No need for (frequent) monitoring and dose adjustment	Missed dose can increase the risk of stroke
Absence of food interactions (no dietary restrictions, enhanced lifestyle)	No routine coagulation monitoring may facilitate non-compliance
Limited drug interactions (simplifies therapy)	No coagulation assay easily available to precisely measure anticoagulation effect*
Rapid onset of action and relatively short half-life periods (convenient around procedures; no need for bridging)	Not approved in valvular AF and end-stage kidney disease
Targeted action - reduced risk of associated effects	Higher cost for patients†
	Long term adverse effects not fully known yet

* Situations which may warrant precise measurement of anticoagulation effect with the NOACs include unexpected thrombotic or bleeding event during treatment, evaluation for urgent surgery, kidney failure with impaired drug clearance, suspected drug overdose, suspected noncompliance, uncertain GI absorption, risk factor profile (weight, advanced age) that could affect dosing, evaluation for tPA therapy for acute stroke.

† Given the non-requirement for frequent laboratory control and dose-adjustment with the NOACs as well as their efficacy and safety profile, overall all of the NOACs are cost-effective in comparison to VKAs.

Table 3. Pharmacological characteristics of warfarin and non-VKA oral anticoagulants [7,29]

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Inhibition of VKORC1	Direct thrombin inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible
Onset of action	Slow, indirect inhibition of clotting factor synthesis	Fast	Fast	Fast	Fast
Offset of action	Long	Short	Short	Short	Short
Absorption	Rapid	Rapid, acid-dependent	Rapid	Rapid	Rapid
Bioavailability, %	>95	6.5	>80	>50	62
T_{max}, hour	2.0-4.0	1.0-3.0	2.5-4.0	1.0-3.0	1.0-2.0
V_d, L	10	60-70	50-55	21	>300
Protein binding, %	99	35	95	87	40-59
$T_{1/2\beta}$, hour	40	12-17	9-13	8-15	9-11
Renal excretion	None	80	35	27	50
Non-renal excretion	None	20	65	73	50
CL/F, L/hour	0.35	70-140	10	5	30.2-33.7
Accumulation in plasma	Dependent on CYP2C9 metabolic efficiency	None	None	1.3-1.9	Negligible
Food effect	No effect on absorption; dietary vitamin K influence on pharmacodynamics	Delayed absorption with food with no influence on bioavailability	Delayed absorption with food with increased bioavailability	None	None
Age	Yes, lower CL/F as age increases	Yes, lower CL/F as age increases	None	Yes, lower CL/F as age increases	NR
Body weight	Yes, higher dose for increased weight	None	None	Yes, higher exposure with low body weight (< 60 kg)	Yes, higher exposure with low body weight (< 60 kg)
Sex	Yes, lower CL/F in women	Yes, lower CL/F in women	None	Yes, higher exposure in women	Minimal
Ethnicity	Lower dose in Asian patients; higher dose in African-American patients	None	Lower dose in Japanese patients	None	None
Drug transporter	None	P-gp	P-gp, BCRP	P-gp, BCRP	P-gp
CYP-mediated	CYP2C9, CYP3A4,	None	CYP3A4/5, CYP2J2	CYP3A4/5, CYP2J2	CYP3A4 (4%)

metabolism	CYP2C19, CYP1A2		(equal)	(minor), CYP1A2 (minor)	
Drug-drug interactions*	Numerous	Potent P-gp inhibitors (verapamil, reduce dose; dronedarone: avoid) and inducers (avoid)	Potent CYP3A4 and P-gp inhibitors (avoid) and inducers (use with caution)	Potent CYP3A4 and P-gp inhibitors (avoid) and inducers (use with caution)	Potent P-gp inhibitors (reduce dose) and inducers (avoid)
Coagulation measurement	INR	TT, dTT, aPTT, ECA	PT, anti-FXa	anti-FXa	PT, aPTT, anti-FXa
Reversal agents	Vitamin K (slow reversal, prolonged inhibition), FFP or PCCs (rapid reversal)	Activated charcoal or haemodialysis (overdose); PCCs or recombinant FVII (uncontrolled bleeding)	Activated charcoal, FFP, PCCs, activated FVII	Activated charcoal, FFP, PCCs, activated FVII	Activated charcoal, FFP, PCCs, activated FVII
Dosing for AF	Individualised for each patient according to INR response (0.5-16 mg qd)	150 mg bid or 110 mg bid in high bleeding risk Contraindicated if CrCl < 30 mL/min†	20 mg qd if CrCl > 50 mL/min or 15 mg qd if CrCl 15-50 mL/min	5 mg bid or 2.5 mg bid if • CrCl 15-29 mL/min or • any 2 of the following are present: ○ age ≥ 80 years ○ body weight ≤ 60 kg ○ serum creatinine ≥ 133 φmol/L	Awaiting EMA and FDA approval‡

AF, atrial fibrillation; aPTT, activated partial thromboplastin test; BCRP, breast cancer resistance protein; bid, twice daily; CL/F, apparent clearance; CrCl, creatinine clearance; CYP, cytochrom P450 isozymes; dTT, diluted thrombin test; ECT, ecarin chromogenic assay; EMA, European Medicines Agency; F, factor; FFP, fresh frozen plasma; INR, international normalized ratio; NR, not reported; qd, once daily; PCC, prothrombin complex concentrate; P-gp, permeability glycoprotein; PT, prothrombin time; Tmax, time to maximum plasma concentration; TT, thrombin time; T1/2β, terminal half-life, Vd, volume of distribution; VKORC1, vitamin K epoxide reductase enzyme subunit 1.

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, and phenytoin. Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort

† FDA approved administration of dabigatran 75 mg bid to patients with CrCl 15-30 mL/min
‡ in the ENGAGE AF-TIMI 48 two dosages were tested: 30 mg qd and 60 mg qd, reduced to 15 mg qd and 30 mg qd, respectively, if any of the following were present: CrCl 30-50 ml/min, body weight ≤60 kg, or concomitant use of verapamil or quinidine

Table 4. Summary of pivotal clinical trials of non-VKA oral anticoagulants in patients with non-valvular AF

Clinical trial	RE-LY[30,31]		ROCKET AF[32]	ARISTOTLE[33]	ENGAGE AF - TIMI 48[34]	
Non-VKA OAC examined	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
Trial design	PROBE		Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy	
Patients	18113		14 264	18 201	21105	
Age, years	71		73	70	72	
Mean $CHADS_2$ score	2.1		3.5	2.1	2.8	
Non-VKA OAC dosing arm	110 mg bid	150 mg bid	20 (15) mg qd	5 (2.5) mg bid	30 (15) mg qd	60 (30) mg qd
Prior vitamin K antagonist treatment, %	50		62	57	59.2	58.8
Prior stroke or transient ischemic attack, %	20 (including SE)		55	19 (including SE)	28.5	28.1
Mean TTR, warfarin arm; %	64		55	62	68.4	
Discontinuation rate, %	21.2 vs 16.6	20.7 vs 16.6	23.9 vs 22.4	25.3 vs 27.5	33.0 vs 34.5	34.4 vs 34.5
Hazard ratios (95% CI) for NOACs versus warfarin						
Stroke or systemic embolism	0.90 (0.74-1.10)	0.65 (0.52-0.81)	0.88 (0.75-1.03)	0.79 (0.66-0.96)	1.13 (0.96-1.34)	0.87 (0.73-1.04)
Ischaemic stroke	1.11 (0.89-1.40)*	0.76 (0.60-0.98)*	0.94 (0.75-1.17)	0.92 (0.74-1.13) §	1.41 (1.19-1.67)	1.00 (0.83-1.19)
Haemorrhagic stroke	0.31 (0.17-0.56)	0.26 (0.14-0.49)	0.59 (0.37, 0.93)	0.51 (0.35-0.75)	0.33 (0.22-0.50)	0.54 (0.38-0.77)
Systemic embolism	1.26 (0.57—2.78)†	1.61 (0.76-3.42)†	0.23 (0.09, 0.61)	0.87 (0.44-1.75)	1.24 (0.72-2.15)	0.65 (0.34-1.24)
All-cause mortality	0.91 (0.80-1.03)	0.88 (0.77-1.00)	0.85 (0.70-1.02)	0.89 (0.80-0.998)	0.87 (0.79-0.96)	0.92 (0.83-1.01)
Cardiovascular mortality	0.90 (0.77-1.06)	0.85 (0.72-0.99)	0.89 (0.73, 1.10)	0.89 (0.76-1.04)	0.85 (0.76-0.96)	0.86 (0.77-0.97)
Myocardial infarction	1.29 (0.96-1.75)	1.27 (0.94-1.71)	0.81 (0.63-1.06)	0.88 (0.66-1.17)	1.19 (0.95-1.49)	0.94 (0.74-1.19)
Major bleeding	0.80(0.70-0.93)	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.47 (0.41-0.55)	0.80 (0.71-0.91)
Major or clinically relevant nonmajor	NA	NA	1.03 (0.96-1.11)	0.68 (0.61-0.75)	0.62 (0.57-0.67)	0.86 (0.80-0.92)

bleeding						
Intracranial hemorrhage	0.30 (0.19-0.45)	0.41 (0.28-0.60)	0.67 (0.47-0.93)	0.42 (0.30-0.58)	0.30 (0.21-0.43)	0.47 (0.34-0.63)
Gastrointestinal bleeding	1.09 (0.85-1.39)	1.49 (1.19-1.88)	1.47 (1.20-1.81)	0.88 (0.67-1.14)	0.67 (0.53-0.83)	1.23 (1.02-1.50)
Any bleeding	0.78 (0.74-0.83)	0.91 (0.86-0.97)	NA	0.71 (0.68-0.75)	0.66 (0.62-0.71)	0.87 (0.82-0.92)

ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation; bid, twice daily; CHADS2, congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack (2 points); CI, confidence interval; ENGAGE AF – TIMI 48 Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation – Thrombolysis In Myocardial Infarction 48; NA, data not available; OAC, oral anticoagulant; qd, once daily; PROBE, prospective, randomized, open-label, blinded end point; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF, Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; SE, systemic embolism; TTR, time in therapeutic range.

* ischaemic or uncertain

† pulmonary embolism

Table 5. Summary of outcomes in pivotal trials on efficacy and safety of NOACs versus warfarin in patients with non-valvular AF

Outcomes	Dabigatran 110 mg bid[30,31]	Dabigatran 150 mg bid[30,31]	Rivaroxaban 20 (15) mg qd[32]	Apixaban 5 (2.5) mg bid[33]	Edoxaban 30 (15) mg qd[34]	Edoxaban 60 (30) mg qd[34]
Stroke/systemic embolism	↔	↓	←	↓	→	←
Ischaemic stroke	↔*	↓*	↔	↔*	↑	↔
Haemorrhagic stroke	↓	↓	↓	↓	↓	↓
Systemic embolism	↔†	↔†	↓	↔	↔	↔
All-cause mortality	↔	←	←	↓	↓	←
Cardiovascular mortality	↔	↓	↔	←	↓	↓
Myocardial infarction	→	→	↔	↔	↔	↔
Major bleeding	↓	↔	↔	↓	↓	↓
Major or clinically relevant non-major bleeding	NA	NA	↔	↓	↓	↓
Intracranial bleeding	↓	↓	↓	↓	↓	↓
Gastrointestinal bleeding	↔	↑	↑	↔	↓	↑
Any bleeding	↓	↓	NA	↓	↓	↓

* ischaemic or uncertain
† pulmonary embolism
↑, significantly increased; ↓, significantly decreased; →, trend toward increased; ←, trend towards decreased; ↔, neither significant difference nor trend were observed
NA, data not available; qd, once daily

Table 6. Systematic reviews and meta-analyses on efficacy and safety of NOACs

Review	NOACs	N of included studies	Efficacy and safety end points, HR (95% CI) for NOACs versus warfarin							
			Stroke/SE	Ischemic stroke	Hemorrhagic stroke	All-cause death	Myocardial infarction	Major bleeding	ICH	GI bleeding
Adam et al.[47]	Dabigatran Rivaroxaban Apixaban	3*	NA	0.89 (0.78-1.02)	0.48 (0.36-0.62)	0.88 (0.82-0.96)	NA	0.80 (0.63-1.01)	NA	1.3 (0.97-1.73)
Dentali et al.[48]	Dabigatran Rivaroxaban Apixaban Edoxaban	12†	0.77 (0.70-0.86)	0.92 (0.81-1.04)	NA	0.89 (0.83-0.96)	0.99 (0.85-1.15)	0.86 (0.80-0.93)	0.46 (0.39-0.56)	NA
Lip et al.[49]	Dabigatran‡ Rivaroxaban Apixaban	3	0.86 (0.77-0.95) / 0.79 (0.71-0.88)	0.98 (0.87-1.12) / 0.88 (0.77-1.00)	0.49 (0.37-0.63) / 0.47 (0.36-0.62)	0.89 (0.83—0.96) / 0.88 (0.82-0.95)	0.95 (0.81-1.12) / 0.95 (0.81-1.12)	0.83 (0.77-0.90) / 0.88 (0.81-0.95)	0.47 (0.38-0.57) / 0.49 (0.40-0.60)	NA
Ruff et al.[50]	Dabigatran Rivaroxaban Apixaban Edoxaban	4	0.81 (0.73–0.91)	0.92 (0.83–1.02)	0.49 (0.38–0.64)	0.90 (0.85–0.95)	0.97 (0.78–1.20)	0.86 (0.73–1.00)	0.48 (0·39–0.59)	1.25 (1.01–1.55)

* additional 3 trials on NOACs in VTE included for analysis of bleeding events

† phase II and phase III trials were included

‡ analysis with data from low and high dosages of dabigatran arms being included separately (dabigatran 110 mg bid + other NOACs / dabigatran 150 mg bid + other NOACs)

GI, gastrointestinal; ICH, intracranial haemorrhage; NA, data not available; SE, systemic embolism

Table 7. Consistency of results on the efficacy and safety of NOACs across patient subgroups

Subgroups	Outcomes	Stroke and systemic embolism HR (95% CI) for NOACs versus warfarin				Major bleeding HR (95% CI) for NOACs versus warfarin			
	Drug, dose*	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Rivaroxaban 20 (15) mg	Apixaban 5 (2.5) mg	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Rivaroxaban 20 (15) mg†	Apixaban 5 (2.5) mg
Age[64-66]	<75	0.93 (0.70–1.22)	0.63 (0.46–0.86)	0.95 (0.76-1.19)	1.16 (0.77-1.73) / 0.72 (0.54-0.96) ‡	0.62 (0.50–0.77)	0.70 (0.57–0.86)	0.96 (0.78-1.19)	0.78 (0.55-1.11) / 0.71 (0.56-0.89)†
	≥75	0.88 (0.66–1.17)	0.67 (0.49–0.90)	0.80 (0.63-1.02)	0.71 (0.53-0.95)	1.01 (0.83–1.23) §	1.18 (0.98–1.42) §	1.11 (0.92-1.34)	0.64 (0.52-0.79)
Stroke risk ($CHADS_2$ score)[32,67,68]	0-1	0.98 (0.63-1.51)	0.61 (0.37-0.99)	NA	0.85 (0.57–1.27)	0.65 (0.49 to 0.88)	0.74 (0.56 to 0.99)	NA	0.59 (0.44–0.78)
	2	1.06 (0.74-1.52)	0.61 (0.40-0.92)	0.85 (0.52—1.38)	0.90 (0.66–1.23)	0.90 (0.71 to 1.14)	0.92 (0.72 to 1.17)	0.92 (0.51-1.66)	0.76 (0.60–0.96)
	3-6	0.78 (0.58-1.04)	0.69 (0.51-0.93)	0.76 (0.57-1.01) / 0.95 (0.72—1.24) / 0.88 (0.58-1.34) / 1.49 (0.62-3.59) ¶	0.70 (0.54–0.91)	0.83 (0.66 to 1.03)	1.07 (0.87 to 1.31)	0.67 (0.48-0.93) / 0.78 (0.57-1.07) / 0.95 (0.59-1.51) / 1.0 (0.35-2.88) §	0.70 (0.56–0.88)
Kidney function (CrCl, mL/min)[32,69,70]	>80	0.84 (0.54–1.32)	0.67 (0.42–1.09)	0.94 (0.67-1.31)	0.88 (0.64-1.22)	0.61 (0.44–0.84)	0.84 (0.62–1.13)	0.87 (0.59-1.28)	0.80 (0.61-1.04)
	50-80	0.93 (0.70–1.23)	0.68 (0.50–0.92)	0.85 (0.67-1.08)	0.74 (0.56-0.97)	0.76 (0.62–0.94)	0.91 (0.75–1.11)	0.73 (0.56-0.96)	0.77 (0.62-0.94)
	<50	0.85 (0.59–1.24)	0.56 (0.37–0.85)	0.88 (0.65-1.19)	0.79 (0.55-1.14)	0.99 (0.77–1.28)	1.01 (0.79–1.30)	0.84 (0.58-1.23)	0.50 (0.38-0.66)‡
Symptomatic HF[32,71,72]	Yes	0.99 (0.69-1.42)	0.75 (0.51-1.10)	0.93 (0.75-1.15)	0.55 (0.34–0.91) / 0.98 (0.65–1.49) #	0.83 (0.64-1.09)	0.79 (0.60-1.03)	0.76 (0.59-0.98)	0.81 (0.58–1.14) / 0.62 (0.44–0.88)¶

	No	0.86 (0.67-1.09)	0.61 (0.47-0.79)	0.81 (0.63-1.04)	0.74 (0.57–0.96)	0.79 (0.67-0.94)	0.99 (0.84-1.16)	0.83 (0.62-1.11)	0.77 (0.62–0.94)
Prior history of stroke/TIA[73-75]	Yes	0.84 (0.58–1.20)	0.75 (0.52–1.08)	0.94 (0.77–1.16)	0.76 (0.56–1.03)	0.66 (0.48–0.90)	1.01 (0.77–1.34)	0.97 (0.79–1.19)	0.73 (0.55–0.98)
	No	0.93 (0.73–1.18)	0.60 (0.45–0.78)	0.77 (0.58–1.01)	0.82 (0.65–1.03)	0.85 (0.72–0.99)	0.91 (0.77–1.06)	1.11 (0.92–1.34)	0.68 (0.58–0·80)
Prior use of VKAs[30,32,81]	VKA-experienced	0.87 (0.66-1.14)	0.67 (0.50-0.90)	0.97 (0.78-1.19)	0.73 (0.57, 0.95)	0.75 (0.61-0.92)	0.93 (0.77-1.12)	0.84 (0.66-1.08)	0.66 (0.55, 0.80)
	VKA-naïve	0.94 (0.71-1.25)	0.64 (0.47-0.88)	0.76 (0.59-0.98)	0.86 (0.67, 1.11)	0.88 (0.73-1.07)	0.95 (0.78-1.15)	0.72 (0.53-0.97)	0.73 (0.59, 0.91)
Antiplatelet agents concomitantly[3,2,76,77]	Yes	0.93 (0.70-1.25)	0.8 (0.59-1.08)	NA	0.58 (0.39-0.85) **	0.82 (0.67-1.0)	0.93 (0.76-1.12)	NA	0.77 (0.60-0.99) **
	No	0.87 (0.66-1.15)	0.52 (0.38-0.72)	NA	0.84 (0.66-1.07) **	0.79 (0.64-0.96)	0.94 (0.78-1.15)	NA	0.65 (0.55-0.78) **
Centre average TTR[78-80]	<LQ	1.00 (0.68–1.45)	0.57 (0.37–0.88)	0.70 (0.47-1.04)	0.73 (0.53–1.00)	0.65 (0.48–0.89)	0.71 (0.52–0.96)	0.80 (0.66-0.98)	0.50 (0.36-0.70)
	LQ-Me	0.81 (0.56–1.17)	0.50 (0.33–0.77)	0.90 (0.64-1.26)	0.94 (0.67-1.31)	0.82 (0.63–1.06)	0.81 (0.62–1.05)	0.96 (0.81-1.14)	0.64 (0.48-0.86)
	Me-UQ	0.89 (0.58–1.36)	0.69 (0.44–1.09)	0.88 (0.62-1.25)	0.64 (0.42-0.97)	0.83 (0.62–1.11)	1.13 (0.87–1.48)	1.03 (0.87-1.22)	0.85 (0.65-1.11)
	>UQ	0.92 (0.59–1.45)	0.95 (0.61–1.48)	0.73 (0.50-1.06)	0.88 (0.57–1.35)	0.90 (0.67–1.21)	1.16 (0.88–1.54) §	1.25 (1.10-1.41) §	0.75 (0.58-0.97)
Patients who underwent cardioversion during follow-up[84-86]		1.28 (0.35–4.76)	0.49 (0.09–2.69)	1.38 (0.61–3.11) ††	No events	2.82 (0.90–8.82)	0.99 (0.25–3.93)	1.51 (1.12–2.05) ††	Only 2 events, one in each group

* hazard ratios for edoxaban according to different subgroups were published as forest plots only

† major or clinically relevant non-major bleeding

‡ for age subgroups <65 / 65 to <75 years

§ significant interaction between subgroups
¶ for $CHADS_2$ score 3/4/5/6
# HF with reduced ejection fraction / HF with preserved ejection fraction
** Patients on aspirin ≥165 mg per day and those who required treatment with both aspirin and a P2Y12 receptor antagonist at baseline were not eligible to be enrolled in ARISTOTLE
†† cardioversion and catheter ablation of AF in total
CrCl, creatinine clearance; HF, heart failure; LQ, low quartile; Me, median; NA, data not available; TIA, transient ischaemic attack; UQ, upper quartile; VKA, vitamin K antagonists

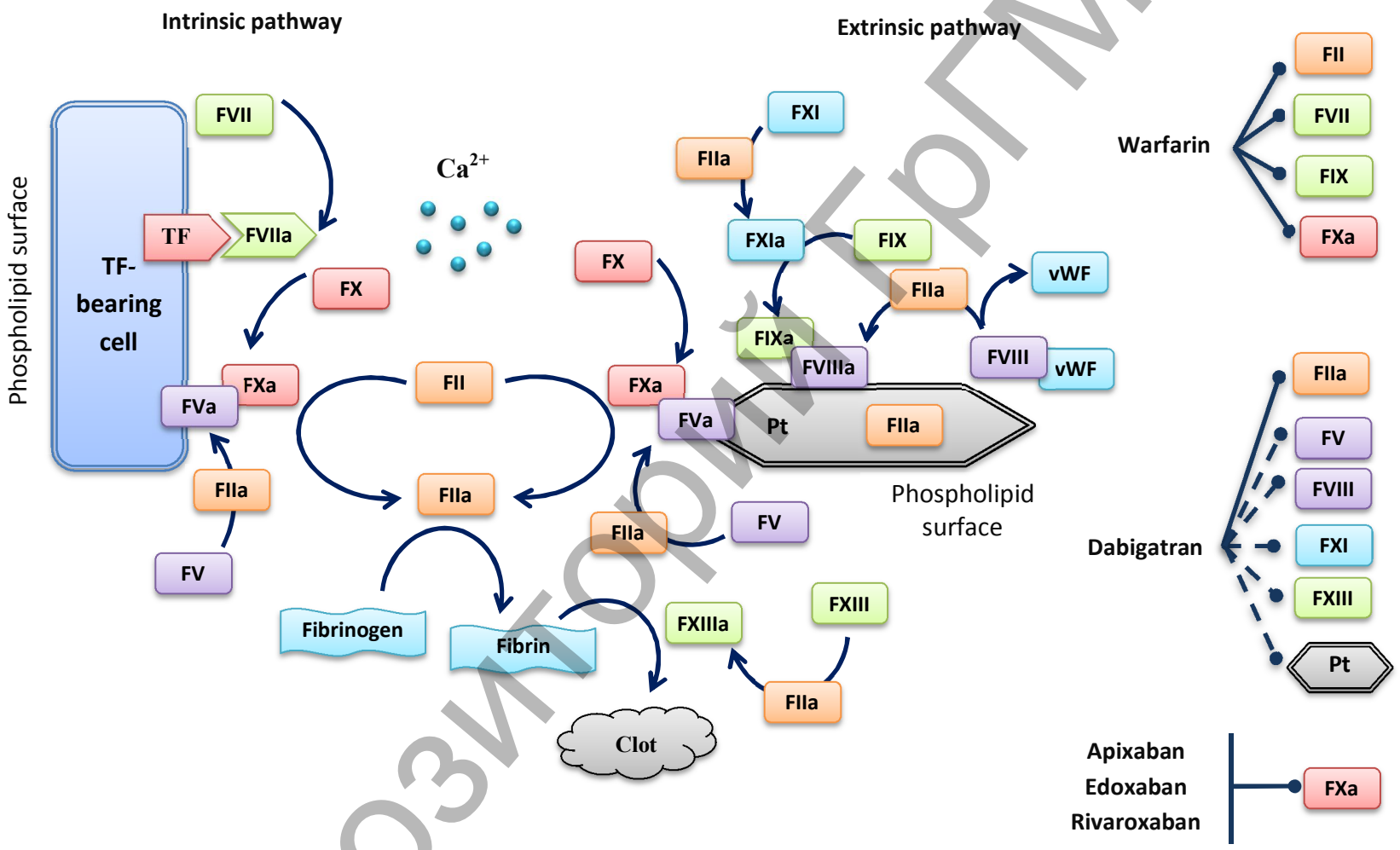

Figure 1. Coagulation cascade and application points for warfarin and NOACs[27]

Solid line, affects synthesis or inhibit in direct way; dashed line, affects activation via thrombin inhibition; F, factor; Pt, platelet; TF, tissue factor; vWF, von Willebrand factor